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(71) Applicant *(for all designated States except US)*: **DEVGEN NV** [BE/BE]; Technologiepark 9, B-9052 Ghent-Zwijnaarde (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ZWAAL, Richard** [NL/BE]; Devgen NV, Technologiepark 9, B-9052 Gent-Zwijnaarde (BE). **KALETTA, Titus** [AT/BE]; Devgen NV, Technologiepark 9, B-9052 Gent-Zwijnaarde (BE). **VAN DEN CRAEN, Marc** [BE/BE]; Devgen NV, Technologiepark 9, B-9052 Gent-Zwijnaarde (BE). **LOGGHE, Marc** [BE/BE]; Devgen NV, Technologiepark 9, B-9052 Gent-Zwijnaarde (BE). **SMITS, Elke** [BE/BE]; Devgen NV, Technologiepark 9, B-9052 Gent-Zwijnaarde (BE). **VAN CREIKINGE, Wim** [BE/BE]; Devgen NV, Technologiepark 9, B-9052 Gent-Zwijnaarde (BE). **BOGAERT, Thierry** [BE/BE]; Devgen NV, Technologiepark 9, B-9052 Gent-Zwijnaarde (BE).

(74) Agents: **BOULT WADE TENNANT** et al.; Verulam Gardens, 70 Gary's Inn Road, London WC1X 8BT (GB).

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(54) Title: METHODS FOR IDENTIFYING PESTICIDAL COMPOUNDS

(57) Abstract: The invention is concerned with methods for use in the identification of compounds having potential utility as pesticides. In particular, the invention relates to methods for use in identifying compounds which affect the activity of a physiologically important calcium pump, the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA).

Methods for identifying pesticidal compounds

The invention is concerned with methods for use in the identification of compounds having potential utility as pesticides. In particular, the invention relates to methods for use in identifying compounds which affect the activity of a physiologically important calcium pump, the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA).

Although a lot of effort has been made over the past few years in the development of novel pesticides there is still a great demand for new pesticides. One of the main problems facing the agrochemical industry at present is the development of pesticide resistance by target organisms. To handle problem, various resistance action committees have been set up within the Global Crop Protection Federation (GCPF, Avenue Louise 143, 1050 Brussels, Belgium). The insecticide resistance committee (IRAC), reports regularly on the emergence of new resistance of insects against insecticides. The results of a resistance survey carried out in 1996, published in "The Pest Manual, 11th edition, ed CDS Tomlin", by the British Crop Protection Council, 49 Downing Street, Farnham, Surrey, GU9 7PH, UK, indicating the problems that exist with insect resistance and hence the need to develop new insecticides.

The Fungicide resistance action committee (FRAC) has already indicated that well known fungi have already developed resistance to well known fungicides such as benzimidazoles, dicarboximides, phenylamides, sterol biosynthesis inhibitors. In 1996 and 1994, the stobilurins and the anilinopyrimidines were introduced on the market as novel fungicides. At the time of publication of the 11th Edition of "The Pest Manual", ibid, no resistance has been observed against those to classes of compounds, but one may expect that in the

near future fungi will also develop resistance against these fungicides.

The herbicide resistance action committee (HRAC) also publishes regularly the present status of herbicide resistance world wide. These publications can be found on HRAC publicity office, C/O David Nevill & Derek Cornes, Novartis protection AG, 4002, Basel Switzerland. The results of these surveys indicate that there is a need for novel herbicides.

A similar pattern of emerging resistance is also observed for other classes of pesticides, particularly rodenticides, acaricides and nematocides. An overview of all such compounds with pesticide activity can be found in "The pest manual", ibid, and in references cited therein; Insecticides with Novel Modes of action, Mechanisms and application, Springer-Verlag Berlin, eds. I. Ishaaya, and D. Degheele. Recently, completely new insecticides have been isolated, such as paralysins (Chiou et al., Biochem. and Biophys. Res. Com. 1998 246:457-462), deoxyribonucleosides and derivatives (Balzarini et al, Mol. Pharmacology. 2000, 57:811-819).

New pesticides should be developed to further protect food production, but should have a minimal impact on the health of human populations and domestic animals and a minimal impact on the ecosystem. Hence, there is a great demand for safer, more selective pesticides affecting only specifically harmful pest species.

The present inventors have identified the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) as a potential target for pesticidal intervention. The SERCA proteins belong to the group of ATP-driven ion-motive ATPases, which also includes, amongst others, the plasma membrane Ca^{2+}-transport ATPases (PMCA), the Na^{+}-K^{+}-ATPases, and the gastric H^{+}-K^{+}-ATPases. SERCA proteins are present in all higher organisms,

including pest species. The evolutionary conservation of SERCA proteins identifies these proteins as an interesting target for pesticidal intervention. Furthermore, it is known that inhibition or deletion of SERCA activity in a variety of organisms results in lethality, or at least a marked reduction in the vitality of the organism. In particular, the present inventors have shown that inhibition of SERCA activity in the nematode *C. elegans* results in lethality. Inhibition of SERCA activity, and hence depletion of endoplasmic reticulum calcium stores also results in a lowering of muscle relaxation and hence immobility and/or respiration deficiency.

The maintenance of high calcium concentrations in the ER is important for the proper synthesis of proteins, including translation, folding, glycosylation, processing and transport. Treatment of living organisms with chemicals that down-regulate or inhibit the activity of SERCA will hence have a negative effect on the welfare of these organisms. As such, SERCA inhibitors are potential pesticides or can be considered as basic compounds for the development of pesticides such as herbicides, insecticides and nematocides. It has been shown that SERCA function is essential in the intracellular trafficking of the Notch receptor in drosophila (Periz et al., 1999 EMBO J; 5983-5993). This study and others indicate that SERCA is an interesting target for pesticidal intervention.

The inventors have developed generic screening methods which may be used to identify compounds which down-regulate SERCA activity and may therefore have the potential to kill pests. Several of these screens are performed in microscopic nematode worms such as *Caenorhabditis elegans*. *C. elegans* is a small roundworm that has a life cycle of only three days, allowing rapid accumulation of large quantities of

individual nematodes. *C. elegans* may be used in the development of high throughput live animal compound screens in which nematodes are exposed to the compound under test and any resultant phenotypic and/or behavioural changes are recorded. The present inventors have developed a number of *C. elegans*-based screening methods which may be used to identify compounds which modulate the activity of SERCA. Furthermore, these *C. elegans* based screening methods may also be used to identify compounds which modulate the activity of other proteins in the SERCA pathway, such as proteins involved in the calcium homeostasis of the cell.

Therefore, in a first aspect the invention provides a method of identifying compounds having pesticidal activity, which method comprises:

providing microscopic nematode worms expressing a pest SERCA protein, said protein being derived from a pest species, other than the *C. elegans* SERCA protein; and

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the microscopic nematode worm in the presence or absence of test compounds;

wherein a reduction in SERCA activity in the presence of a compound is taken as an indication that the compound has pesticidal activity.

The method of the invention may be used to identify compounds which have pesticidal activity because they directly or indirectly affect the activity of the SERCA protein. Hence, the invention further provides a method of identifying compounds capable of down-regulating the activity of a sarco/endoplasmic reticulum calcium ATPase, which

method comprises:

providing microscopic nematode worms expressing a pest SERCA protein, said protein being derived from a pest species, other than the *C. elegans* SERCA protein;

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the microscopic nematode worm in the presence or absence of test compounds; and

thereby identifying compounds capable of down-regulating the activity of SERCA.

The preferred microscopic nematode species for use in the screening methods of the invention is *Caenorhabditis elegans*. It will, however, be appreciated that the methods may be carried out with other nematodes and in particular with other microscopic nematodes, preferably microscopic nematodes belonging to the genus *Caenorhabditis* including *C. briggsae*. As used herein the term "microscopic" nematode encompasses nematodes of approximately the same size as *C. elegans*, being of the order 1mm long in the adult stage. Microscopic nematodes of this approximate size are extremely suited for use in mid- to high-throughput screening as they can easily be grown in the wells of a multi-well plate of the type generally used in the art to perform such screening.

C. elegans occurs naturally in the soil but can be easily grown in the laboratory on nutrient agar inoculated with bacteria, preferably *E. coli,* or in liquid culture. Each worm grows from an embryo to an adult worm of about 1 mm long in three days or so. As it is fully transparent at all stages of its life, cell divisions, migrations and differentiation can be seen in live animals. Furthermore, although its anatomy is simple its somatic cells represent most

major differentiated tissue type including muscles, neurons, intestine and epidermis. Accordingly, differences in phenotype which represent a departure from that of wild-type *C. elegans* are relatively easily observed and many phenotypic, physiological or biochemical characteristics of the nematode submit to quantitative measurement.

In the context of this application, the term "pest SERCA protein" encompasses any SERCA protein derived from a pest species. The term "pest species" encompass species recognised as such by one skilled in the art. Pest species include, but are not necessarily limited to, arthropods such as insects, ticks, mites, spiders and nematodes (excluding *C. elegans* for the purposes of this application) and also fungi, plants and rodents. The term "pest species" also encompasses parasitic pest species, including human parasites, and the term "compounds having pesticidal activity" is to be interpreted accordingly as encompassing compounds having anti-parasitic activity which may have utility in the pharmaceutical and/or veterinary fields. A non-exhaustive list of pest species is included in the accompanying Examples. Further lists of pest species can be found in "The Pest Manual", ed CDS Tomlin, BCPC.

The term "compounds having pesticidal activity" is to be interpreted as encompassing compounds which are lethal to one or more pest species as hereinbefore defined or lethal to the progeny of such a pest species. As aforesaid, this definition encompasses compounds having anti-parasitic activity.

The term "SERCA protein derived from a pest species" is intended to encompass any SERCA protein naturally expressed by a pest species, including naturally occurring splice variants, allelic variants and isoforms. Many species express more than one

SERCA isoform and the scope of the invention is not restricted to any particular isoform.

The term "SERCA protein derived from a pest species" is also intended to encompass specific mutant versions of naturally occurring pest SERCA proteins, including, for example, mutant proteins engineered by directed mutagenesis techniques. Specific mutant pest SERCA proteins will advantageously retain near wild-type SERCA ATPase activity.

Further examples of "SERCA proteins derived from a pest species" within the scope of the invention are chimeric proteins created by in-frame fusion of fragments of two or more SERCA proteins, at least one of which is a SERCA protein derived from a pest species. Chimeric proteins included within this definition include fusions of a pest SERCA protein and a *C. elegans* SERCA protein (see accompanying Examples).

The microscopic nematode worm expressing the pest SERCA protein may, advantageously, be a transgenic worm containing a transgene comprising nucleic acid encoding the pest SERCA protein operably linked to a promoter. In the context of this application the term "transgene" refers to a DNA construct comprising a promoter operably linked to a DNA sequence encoding the pest SERCA protein. The construct may contain additional DNA sequences in addition to those specified above. The transgene may, for example, form part of an expression vector, such as plasmid vector. By the term "operably linked" it is to be understood that the promoter is positioned to drive transcription of the protein-encoding DNA fragment.

Methods of preparing transgenic *C. elegans*, including *C. elegans* carrying multiple transgenes, are well known in the art and are described, for example, by Craig Mello and Andrew Fire, Methods in Cell Biology, Vol 48, Ed. H.F. Epstein and D.C. Shakes,

Academic Press, pages 452-480. A typical approach involves the construction of a plasmid-based expression vector in which a protein-encoding DNA of interest is cloned downstream of a promoter having the appropriate tissue or cell-type specificity. The plasmid vector is then introduced into *C. elegans* of the appropriate genetic background, for example using microinjection. In order to facilitate the selection of transgenic *C. elegans* a second plasmid carrying a selectable marker may be co-injected with the experimental plasmid.

Plasmid vectors are usually maintained in cells of transgenic *C. elegans* in the form of an extrachromosomal array. Although plasmid vectors are relatively stable as extrachromosomal arrays they can alternatively be stably integrated into the *C. elegans* genome using standard technology, for example, using gamma ray-induced integration of extrachromosomal arrays (methods in Cell Biology, Vol 48 page 425-480).

The DNA sequence encoding the pest SERCA protein may be any DNA sequence comprising the complete open reading frame of the corresponding pest SERCA gene, such as, for example, a fragment of genomic DNA or cDNA. A number of pest SERCA cDNA sequences are available from publicly accessible sequence databases such as the GenBank database. The number of sequences deposited in the publicly accessible sequence databases is increasing all the time and these sequences are derived from an increasing diversity of species. A list of database accession numbers is provided in the accompanying Examples. Using this sequence data it is a matter of routine to clone a corresponding cDNA using molecular biology techniques well known in the art (see 'Current Protocols in Molecular Biology', Ed Ausubel et al., John Wiley & Sons, Inc). Specific examples of the cloning of pest

SERCA cDNAs based on sequence data accessed from the database are included herein.

The inventors have developed an approach to isolate SERCA cDNAs from various other pest species, in particular pest species for which no or limited sequence data is available through database sources. The inventors' method is generally applicable and comprises the following steps:

a) Prepare a multiple alignment of known pest SERCA protein sequences (for example using ClustalW software);

b) Identify blocks of homology (for example using the Block Maker software accessible via the Blocks WWW Server at the Fred Hutchinson Cancer Research Center, Seattle, Washington, USA http://blocks.fhcrc.org);

c) Design degenerate oligonucleotide primers to conserved regions of amino acid sequence (for example using CODEHOP (Rose, *et al.*, NAR 26: 1628-1635);

d) Perform PCR using pairs of degenerate primers on cDNA prepared from the pest species;

e) Clone PCR fragments into a suitable cloning vector (many vectors suitable for the cloning of PCR products are available commercially);

f) Isolate full length cDNA corresponding to the PCR fragment (for example using 5' and 3' RACE or cDNA library screening, techniques which are well known in the art).

By way of illustration of this approach, a homology series of plant SERCA proteins used to identify degenerate primers and primer combinations to

isolate SERCA cDNAs from plant pests is shown in the accompanying Figure 1. A more general homology series of SERCA proteins from more diverse species is shown in Figure 2. This alignment may be used to design degenerate primers useful in the isolation of SERCA proteins from more diverse pest species. A list of primers and primer combinations is included in the accompanying Examples.

The promoter part of the transgene may be any promoter which is capable of directing gene expression in the nematode. Preferably the DNA encoding the pest SERCA protein is operably linked to the promoter region of a SERCA gene. Most preferably the promoter region of the *C. elegans sca-1* gene is used. The term 'promoter region' as used herein refers to a fragment of the upstream region of a given gene which is capable of directing a pattern of gene expression substantially identical to the natural pattern of expression of the given gene.

When the screen is carried out using transgenic *C. elegans*, the promoter may, advantageously, be the promoter region of a *C. elegans* gene and may be a tissue-or cell type-specific promoter. With the use of a promoter of appropriate specificity, the pest SERCA protein can be expressed in all the cells of *C. elegans*, in a given type of tissue (i.e. all muscles), in a single organ or tissue (for example, the pharynx or the vulva), in a subset of cell types, in a single cell type or even in a single cell. Tissue-specific *C. elegans* promoters which may be used in accordance with the invention include the myo-2 promoter which directs gene expression in the pharynx, the myo-3 promoter which directs gene expression in the body wall muscles, the egl-15 and ceh-24 promoters which direct gene expression in vulva muscles. Other tissue-specific *C. elegans* promoters are well known to

persons skilled in the art.

In order to screen for compounds which act specifically on the expressed pest SERCA protein, rather than the endogenous nematode SERCA protein, it is preferred to use nematodes which, at the same time as expressing the pest SERCA protein, exhibit no or substantially reduced activity of the endogenous nematode SERCA protein in one or more tissues or cell types. *C. elegans* has a single SERCA gene, which was identified by the *C. elegans* genome-sequencing consortium (see Science issue 282, 1998). The *C. elegans* SERCA gene, designated *sca-1*, is located on chromosome III on a cosmid named K11D9. On a physical level, the gene consists of seven exons that span an Open Reading Frame of 3.2 kb, resulting in a predicted protein of 1059 amino acids. The consensus alternative splice site that is present in the C-terminal end of mammalian SERCA genes is also present in *C. elegans*. This leads to a second isoform consisting of eight exons that span an ORF of 3.0kb, resulting in a protein of 1004 amino acids.

In the context of this application the term 'activity' used in relation to a SERCA protein refers to the calcium ATPase activity of the protein, unless otherwise stated. There are various ways in which the activity of the endogenous nematode SERCA protein can be substantially reduced or abolished. In one embodiment, this is achieved by introducing the transgene encoding the pest SERCA protein into a mutant strain which exhibits no or substantially reduced activity of the endogenous SERCA protein in one or more tissues or cell types. This mutant strain may carry a knock-out or loss-of-function mutation in the chromosomal SERCA gene. Alternatively, the mutation may abolish/reduce SERCA activity through a down-regulation of SERCA expression in one or more

cell types or tissues or a defect in regulation of the activity of the SERCA protein.

C. elegans having a reduction-of-function mutation or a knock-out mutation in the *sca-1* gene can be isolated using a classical non-complementation screen, starting with a heterozygote *C. elegans* strain carrying a mutant *sca-1* allele on one chromosome and a recessive marker close to the wild-type *sca-1* allele on the other chromosome. The nematodes are subjected to mutagenesis using standard techniques (EMS or UV-TMP are suitable for this purpose) and the progeny is screened by eye for defects, especially in tissues which express SERCA. Since the screening is performed in the F1 generation, mutations will only give rise to a phenotype if the mutation occurs in the *sca-1* gene (due to non-complementation) or if the mutation is dominant, which does not occur frequently. These two possibilities can be distinguished in subsequent generations. A newly introduced *sca-1* mutation should be linked to the recessive marker. As a further control, DNA sequencing can be performed to determine the nature of the mutation.

An example of a *C. elegans* strain which carries a knock-out mutation in the *sca-1* gene is strain *ok190*, described in the accompanying Examples. A protocol for introducing a pest SERCA transgene onto an sca-1 knock-out genetic background is included in the accompanying examples.

In another embodiment, activity of the endogenous nematode SERCA protein can be reduced by specifically down-regulating the expression of the SERCA protein in one or more tissues using antisense techniques or double-stranded RNA inhibition (RNAi). This can be achieved by transfection of the nematode, preferably *C. elegans*, with a vector that expresses either an antisense SERCA RNA or a double-stranded SERCA RNA.

The antisense or double-stranded SERCA RNA should be capable of selectively inhibiting expression of the endogenous nematode SERCA protein but not the pest SERCA protein.

Specific down-regulation of SERCA expression in different cell types or tissues of the nematode can be achieved by incorporating into the vector an appropriate tissue-specific promoter to drive expression of the antisense RNA or double stranded RNA in the required tissues. SERCA expression will be specifically down-regulated only in those tissues which express the antisense RNA or double stranded RNA. By way of example, the promoter region of the *C. elegans sca-1* gene itself can be used to direct expression of an antisense RNA or double stranded RNA in all the cells and tissues of *C. elegans* which express endogenous SERCA. The *C. elegans myo-2* promoter can be used to direct expression in the pharynx. The *C. elegans myo-3* promoter can be used to direct expression in the body wall muscles. The use of antisense and double stranded RNA inhibition will be further understood with reference to the Examples included herein.

RNAi technology is well known in the *C. elegans* field as a tool for inhibiting expression of a specific target gene in *C. elegans,* as described by Fire et al., Nature 391:801-811 (1998) and Timmins and Fire, Nature 395:854 (1998). The standard approach is based on injection of dsRNA directly into the worm. Alternative RNAi techniques which may be used to inhibit SERCA activity are described in the applicant's International patent application No. WO 00/01846. These techniques, which are based on delivery of dsRNA to *C. elegans* by feeding with an appropriate dsRNA or feeding with food organisms which express an appropriate dsRNA, may lead to a more

stable RNAi phenotype than results from injection of dsRNA.

In a further embodiment, a pest SERCA-specific screen may be performed by using transgenic *C. elegans* expressing a pest SERCA protein which is resistant to a chemical inhibitor of SERCA activity, such as thapsigargin. The pest SERCA protein may be variant carrying a mutation in the thapsigargin binding site The mutation Phe259Val renders *C. elegans* SERCA resistant to inhibition with thapsigargin. Equivalent mutations may be introduced into transgenes encoding pest SERCA proteins using standard site-directed mutagenesis. An alignment of SERCA amino acid sequences, such as that shown in Figure 2, may be used to locate the amino acid residue in the pest SERCA protein which is equivalent to residue Phe 259 of *C. elegans* SERCA. Applying the SERCA inhibitor, for example thapsigargin, to transgenic *C. elegans* which express a resistant mutant pest SERCA will result in inhibition of the endogenous *C. elegans* SERCA only. Thus, if the inhibitor is added to the screening assay in addition to the test compound, the screen will be specific for the pest SERCA.

The invention also encompasses an embodiment of the screening method in which the pest SERCA protein is specifically expressed in a tissue or cell type of the nematode which exhibits no or only minor background activity of the endogenous *C. elegans* SERCA protein. In this case it is not necessary to reduce/abolish activity of the endogenous nematode SERCA protein in order to screen selectively on the pest SERCA protein.

An example of a nematode tissue which exhibits little or no SERCA activity is the neurons. In a preferred embodiment the screen is performed using transgenic *C. elegans* in which expression of a pest

SERCA protein is driven by a neuron-specific promoter. Examples of neuron-specific promoters which may be used in this embodiment of the invention are the unc-119, ser-1, eat-18, acm-1, acm-3 and avr-14 promoters. Other suitable neuron-specific *C. elegans* promoters are known in the art.

The screening methods of the invention rely on detection of an indicator of SERCA activity in the presence or absence of a test compound. There are a number of different phenotypic, behavioural or biochemical indicators of SERCA activity in the nematode which can be used as the basis of the screening method. These include pharynx pumping efficiency, egg laying behaviour, mating behaviour, defecation behaviour, growth rate, movement behaviour, life/death of the nematode and intracellular Ca^{2+} concentration.

The inventors have observed that a reduction in SERCA activity in nematodes such as *C. elegans* results in various phenotypic and behavioural defects. Many of these defects can be used as basis of an assay to isolate compounds that alter the activity of SERCA, and also compounds which affect the activity of other components of the SERCA pathway, such as proteins involved in the calcium homeostasis of the cell. The main defects, and hence phenotypes, associated with reduced SERCA activity are related to muscle function e.g pharyngeal muscle, body wall muscle, vulva muscle, anal repressor muscle, and anal sphincter muscle, as illustrated by the RNAi experiments and thapsigargin inhibition experiments described in the accompanying examples. Screens based on the detection of phenotypic characteristics associated with reduced SERCA activity in these muscles can be used to identify compounds and genes that alter the activity of SERCA. In addition, other phenotypes, such as paleness, reduced growth, reduced progeny, protruding

vulva and protruding rectum can be used to identify compounds and genes that alter the function of SERCA.

In one embodiment, the assay can be based on detection of pharynx pumping efficiency as an indicator of SERCA activity. If the starting nematode strain exhibits a near wild-type rate of pharynx pumping, then a decrease in the rate of pharynx pumping in the presence of a test compound can be used as an indicator of reduction of SERCA activity in the pharynx. In order to use pharynx pumping efficiency as an indicator of the activity of the pest SERCA protein, the pest SERCA protein must be expressed in at least the muscles of the pharynx. Activity of the endogenous nematode SERCA protein should also be abolished or substantially reduced in the pharynx muscles in order to confer specificity for the pest SERCA protein.

C. elegans feeds by taking in liquid containing its food (e.g. bacteria). It then spits out the liquid, crushes the food particles and internalises them into the gut lumen. This process is performed by the muscles of the pharynx. The process of taking up of liquid and subsequently spitting it out, requiring contraction and relaxation of muscles, is called pharyngeal pumping or pharynx pumping.

Alterations in SERCA activity influence the pharyngeal pumping rate. In particular, inhibition of SERCA using thapsigargin causes a reduction in the rate of pharynx pumping. Measurement of the pumping rate of the *C. elegans* pharynx is hence a method to determine the activity of SERCA. Pharynx pumping efficiency can be conveniently measured by placing the nematodes in liquid containing a fluorescent marker molecule precursor, such as calcein-AM. Calcein-AM present in the medium is taken up by the nematodes and the AM moiety is cleaved off by the action of esterases present in the *C. elegans* gut, resulting in

the production of the fluorescent molecule calcein. As the quantity of calcein-AM that is delivered in the gut is dependent on the pumping rate of the pharynx, and hence of the activity of SERCA, calcein fluorescence measured in the gut is a quantitative and qualitative measurement of the SERCA activity. It would be readily apparent to one skilled in the art that other types of marker molecule precursor which are cleavable by an enzyme present in the gut of *C. elegans* to generate a detectable marker molecule could be used instead of calcein-AM with equivalent effect.

In a further embodiment, the assay can be based on detection of changes in the egg laying behaviour of the nematode or on detecting changes in the amount of progeny produced by the nematode as indicators of SERCA activity. For this embodiment, the nematode should express the pest SERCA protein in at least the vulva muscles. Activity of the endogenous nematode SERCA protein should be abolished or substantially reduced in the vulva muscles in order to confer specificity for the pest SERCA protein.

Defects associated with reduced SERCA activity in the vulva muscles include defects in the production and laying of eggs and hence a reduction in the number of progeny produced. Typically, nematodes with reduced SERCA expression in the vulva are not able to lay their eggs. The eggs thus hatch inside the mother, which then dies. These mothers are easy to recognize under the dissection microscope. As a consequence of the egg laying defect, less progeny are produced and hence the culture as a whole grows much more slowly. Defects associated with reduced SERCA activity have also been observed in the gonad, including the sheath cells and the spermatheca. These defects also result in reduced egg formation and hence a reduced egg laying phenotype.

One convenient way in which the egg production

and egg laying behaviour of the nematodes can be monitored is by counting the number of resultant offspring produced. A variety of different techniques can be used for this purpose. For example, the offspring can be measured directly using the growth rate assay and/or the movement assay described below. Alternatively, specific antibodies and fluorescent antibodies can be used to detect the offspring. Any specific antibody that only recognizes eggs, or L1 or L2 or L3 or L4 stage nematodes, will only recognize offspring. By way of example, an antibody that recognizes an antigen on the surface of *C. elegans* L1 larvae has been described by Hemmer *et al.*, (1991) *J Cell Biol*, 115(5): 1237-47. Finally, the number of eggs or offspring in each well can be counted directly using a FANS device. The FANS device is a 'worm dispenser apparatus' having properties analogous to flow cytometers such as fluorescence activated cell scanning and sorting devices (FACS) and is commercially available from Union Biometrica, Inc, Somerville, MA, USA. The FANS device, also designated a nematode flow meter, can be the nematode FACS analogue, described as fluorescence activated nematode scanning and sorting device (FANS). The FANS device enables the measurement of nematode properties, such as size, optical density, fluorescence, and luminescence and the sorting of nematodes based on these properties.

In a still further embodiment, the assay can be based on detection of a change in the defecation behaviour of the nematode as an indicator of SERCA activity. This embodiment is particularly suitable for use when the nematode expresses the pest SERCA protein in the anal sphincter or the anal repressor. In this case, activity of the endogenous nematode SERCA protein should be abolished/reduced in the anal sphincter or anal repressor in order to confer

specificity for the pest SERCA protein.

A reduction in the SERCA activity in the anal sphincter and/or the anal repressor, for example following treatment with thapsigargin, results in nematodes which are constipated and also in nematodes with a protruding rectum. Changes in the defecation rate of the nematodes can therefore also serve as an indicator of SERCA activity.

Defecation rate can be measured using an assay similar to that described above for the measurement of pharynx pumping efficiency, but using a marker molecule which is sensitive to pH. A suitable marker is the fluorescent marker BCECF. This marker molecule can be loaded into the *C. elegans* gut in the form of the precursor BCECF-AM which itself is not fluorescent. If BCECF-AM is added to nematodes growing in liquid medium the nematodes will take up the compound which is then cleaved by the esterases present in the *C. elegans* gut to release BCECF. BCECF fluorescence is sensitive to pH and under the relatively low pH conditions in the gut of *C. elegans* (pH<6) the compound exhibits no or very low fluorescence. As a result of the defecation process the BCECF is expelled into the medium which has a higher pH than the *C. elegans* gut and the BCECF is therefore fluorescent. The level of BCECF fluorescence in the medium (measured using a fluorimeter on settings Ex/Em=485/550) is therefore an indicator of the rate of defecation of the nematodes.

Defecation can also be measured using a method based on the luminescent features of the chelation of terbium by aspirin. The method requires two pre-loading steps, first the wells of a multi-well plate are pre-loaded with aspirin (prior to the addition of the nematodes) and second, bacteria or other nematode food source particles are pre-loaded with terbium

using standard techniques known in the art. *C. elegans* are then placed.in the wells pre-loaded with aspirin and are fed with the bacteria pre-loaded with terbium.

The terbium present in the pre-loaded bacteria added to the wells will result in a low level of background luminescence. When the bacteria are eaten by the nematodes the bacterial contents will be digested but the terbium will be defecated back into the medium. The free terbium will then be chelated by the aspirin which was pre-loaded into the wells resulting in measurable luminescence. The luminescence thus observed is therefore an indicator of nematode defecation.

In a still further embodiment, the assay may be based on the use of growth rate as an indicator of SERCA activity.

It has been observed that a reduction in SERCA activity, for example using inhibition by thapsigargin or double stranded RNA inhibition, results in a reduction in the growth rate of a *C. elegans* culture. Growth rate of the culture as a whole is reduced because the nematodes produce fewer progeny and also because the few progeny that are produced show poor/delayed growth. Cultures of nematodes which produce many healthy progeny grow faster than cultures of nematodes with few and/or sick progeny. Hence measurement of the growth rate of a culture of *C. elegans* is in indication of the activity of SERCA in the individual nematodes of the culture.

Growth rate can be monitored by measuring the number of eggs or the number offspring present in the culture, by measuring the total fluorescence in the culture (this can be autofluorescence, or fluorescence caused by a transgene encoding a flourescent or luminescent protein), but can also be measured using

the movement screen described below. Alternatively, the growth rate of a culture of *C. elegans* can also be assayed by measuring the turbidity of the culture. In order to perform this 'turbidity assay' the nematodes are grown in liquid culture in the presence of *E. coli* or other suitable bacterial food source. As the culture of nematodes grows the food source bacteria will be consumed. The greater the number of nematodes in the culture, the more food source bacteria will be digested. Hence, measurement of the turbidity or optical density of the liquid culture will provide an indirect indication of the number of nematodes in the culture. By taking sequential measurements over a period of time it is possible to monitor the growth rate of the whole *C. elegans* culture.

As an alternative to the above-described methods, the growth rate and amount of progeny can be measured on a plate. Slow growing nematodes, nematodes with vulva defects and nematodes with gonad defects will produce less progeny within a certain time compared to nematodes which do not have these defects. Preferentially, the amount of offspring produced is scored on day five and on day eight. In experiments where the amount of offspring is reduced very drastically due to severe defects in the vulva, gonad or growth rate reduction, the offspring can also be scored at later time intervals.

In a still further embodiment, the assay may be based on detecting changes in the movement behaviour of *C. elegans* as an indicator of SERCA activity. This embodiment is particularly suitable for use when the nematodes express the pest SERCA protein in at least the body wall muscles. At the same time, activity of the endogenous nematode SERCA protein should also be abolished/reduced in at least the body wall muscles in order that the assay is specific for the pest SERCA

protein.

SERCA is widely expressed in the muscles of *C. elegans*, including the muscles of the body wall. A reduction of SERCA activity in the body wall muscles gives rise to nematodes with movement defects. Thus, movement defects can be used as the basis of an assay in which the nematodes are contacted with a compound under test and any changes in the movement behaviour of the nematodes are observed as an indication of SERCA activity. Compounds which cause defective movement behaviour are scored as compounds capable of down-regulating the activity of SERCA.

Changes in the movement behaviour of the nematodes can obviously be detected by visual inspection, but as an alternative a number of non-visual approaches for analysing the movement behaviour of nematodes have been developed which can be performed in a multi-well plate format and are therefore suitable for use in high-throughput screening. Nematode worms that are placed in liquid culture will move in such a way that they maintain a more or less even (or homogeneous) distribution throughout the culture. Nematode worms that are defective in movement will precipitate to the bottom in liquid culture. Due to this characteristic of nematode worms as result of their movement phenotype, it is possible to monitor and detect the difference between nematodes that move and nematodes that do not move. Advanced multi-well plate readers are able to detect sub-regions of the wells of multi-well plates. By using these plate readers it is possible to take measurements in selected areas of the surface of the wells of the multi-well plates. If the area of measurement is centralized, so that only the middle of the well is measured, a difference in nematode autofluorescence (fluorescence which occurs in the absence of any external marker molecule) can be

observed in the wells containing a liquid culture of nematodes that move normally as compared to wells containing a liquid culture of nematodes that are defective for movement. For the wells containing the nematodes that move normally, a low level of autofluorescence will be observed, whilst a high level of autofluorescence can be observed in the wells that contain the nematodes that are defective in movement.

In an adaptation of the movement assay, autofluorescence measurements can be taken in two areas of the surface of the well, one measurement in the centre of the well, and on measurement on the edge of the well. Comparing the two measurements gives analogous results as in the case if only the centre of the well is measured but the additional measurement of the edge of the well results in an extra control and somewhat more distinct results.

As an alternative to the above-described embodiments of the assay which are all based on the observation of changes in phenotypic and/or behavioural characteristics of the nematode as an indicator of SERCA activity, the assay may be based on detection of intracellular Ca^{2+} levels as an indicator of SERCA activity in a given cell type or tissue. This may be accomplished using a marker molecule which is sensitive to changes in intracellular Ca^{2+} such as, for example, apoaequorin.

Aequorin is a calcium-sensitive bioluminescent protein from the jellyfish Aequorea victoria. Recombinant apoaequorin, which is luminescent in the presence of calcium but not in the absence of calcium, is most useful in determining intracellular calcium concentrations and even calcium concentrations in sub-cellular compartments. Expression vectors suitable for expressing recombinant apoaequorin and, in addition, vectors expressing apoaequorin proteins which are targeted to different sub-cellular

compartments, for example the nucleus, the mitochondria or the endoplasmic reticulum are available commercially (e.g. from Molecular probes, Eugene, OR, USA).

As SERCA is a endoplasmic reticulum-localized calcium pump, an apoaequorin that is targeted to the endoplasmic reticulum (hereinafter referred to as erAEQ) is particularly useful for developing assays for SERCA activity. The vector erAEQ/pcDNAI (Molecular Probes) contains an Igγ2b heavy chain gene from mouse, an HA1 epitope and a recombinant apoaequorin in fusion. The mouse gene targets the apoaequorin to the endoplasmic reticulum, and the apoaequorin is mutated to make it less sensitive to calcium, as the concentrations of this ion are relatively high in the endoplasmic reticulum. Although apoaequorin is the calcium sensor of choice, it would be apparent to persons skilled in the art that any other calcium sensor localized in the endoplasmic reticulum could be used with equivalent effect.

Plasmid expression vectors which drive expression of the ER-localized apoaequorin in *C. elegans* can be easily constructed by cloning nucleic acid encoding erAEQ downstream of a promoter capable of directing gene expression in one or more tissues or cell types of *C. elegans*, such that the promoter and the erAEQ-encoding sequence are operably linked. In a typical cloning procedure, the apoaequorin gene in fusion with the signals needed to locate the resulting protein to the endoplasmic reticulum was isolated from erAEQ/pcDNAI by EcoRI digestion and cloned into pBlue2SK. The erAEQ was then isolated as an EcoRI/Acc65I fragment by partial digestion and cloned in the vector pGK13 digested with the same enzymes. pGK13 is a plasmid vector containing a 2915bp fragment of the upstream region of the *C. elegans sca-1* gene.

Suitable promoters which may be included into an expression vector to drive erAEQ expression include the pharynx-specific promoter *myo-2*, the *C. elegans sca-1* promoter which directs expression in a wide range of muscle tissues and the body wall muscle-specific promoter *myo-3*. The vectors can then be used to construct transgenic *C. elegans* according to the standard protocols known to those of ordinary skill in the art. Expression of erAEQ allows for the determination of the calcium levels in the endoplasmic reticulum of various *C. elegans* cells and tissues, using the protocols of the manufacturer of erAEQ, or minor modifications thereof. Alterations in SERCA activity influence the concentration of calcium in the endoplasmic reticulum as SERCA functions as an endoplasmic reticulum calcium pump. Hence the apoaequorin luminescence measured in the assay is directly related to SERCA activity.

To perform a compound screen using one of the aforementioned indicators of SERCA activity nematodes are exposed to a variety of test compounds and compounds are selected which induce a change in the chosen indicator of SERCA activity. In a typical compound screen a plurality of tests may be run in parallel containing different concentrations of the test compound. For comparison purposes a negative control (zero concentration of test compound) may be included. Automated measuring allows the assay to be performed in mid-to-high throughput format. The precise concentration of the candidate compound to be tested in the screening method may vary according to the nature of the compound and such factors as solubility etc. It is advantageous to test a range of concentrations of the candidate compound. Concentrations in the range of about 5 µM to about 2000 µM are generally observed to be suitable. In

general it is desirable to select a concentration which produces a detectable change in the worm as compared to the appropriate negative control (i.e. worms not exposed to the compound), ignoring non-specific effects. It is to be noted that the chosen concentration need not necessarily an amount which would be considered a 'pesticidal' dose.

It is not strictly essential to screen on a pest-derived SERCA protein in order to identify SERCA inhibitors having the potential to kill pests. Screens can also be performed using nematodes which exhibit wild-type activity of the endogenous nematode SERCA protein. Compounds which inhibit the endogenous nematode SERCA protein may also inhibit SERCA proteins from pest species.

Therefore, in a second aspect the invention provides a further nematode-based screening method which does not require the use of a pest-derived SERCA protein. This method comprises steps of:

providing microscopic nematodes which exhibit wild-type activity of the endogenous nematode SERCA protein; and

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the nematodes in the presence or absence of test compounds;

wherein a reduction in SERCA activity in the presence of a compound is taken as an indication that the compound has the potential to kill pests.

This method may also be used to identify compounds which have pesticidal activity because they directly or indirectly affect the activity of the SERCA protein. Therefore, according to this aspect of the invention there is also provided a method of identifying compounds capable of down-regulating the

activity of a sarco/endoplasmic reticulum calcium ATPase, which method comprises:

providing microscopic nematodes which exhibit wild-type activity of the endogenous nematode SERCA protein;

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the nematodes in the presence or absence of test compounds; and

thereby identifying compounds capable of down-regulating the activity of SERCA.

These screening methods are again most preferably carried out using *C. elegans*, although it will be appreciated that the methods could be carried out using other microscopic nematode species.

An example of a *C. elegans* strain which exhibits wild-type SERCA activity is the N2 strain, available from the *C. elegans* Genetic Center (CGC) at the University of Minnesota, St Paul, Minnesota, USA. In a preferred embodiment the screening method may be carried out using the N2 strain. The N2 strain has been particularly well characterised in the literature with respect to properties such as pharynx pumping rate, growth rate and egg laying capacity (see Methods in Cell Biology, Volume 48, Caenorhabditis elegans: Modern biological analysis of an organism, ed. by Henry F. Epstein and Diane C. Shakes, 1995 Academic Press; The nematode Caenorhabditis elegans, ed. by William Wood and the community of *C. elegans* researchers., 1988, Cold Spring Harbor Laboratory Press; *C. elegans* II, ed. by Donald L. Riddle, Thomas Blumenthal, Barbara J. Meyer and James R. Priess, 1997, Cold Spring Harbor Laboratory Press.).

The screening methods may also be carried out using a *C. elegans* strain other than N2 which exhibits

similar SERCA activity to N2. This may be a mutant strain or a transgenic strain.

A range of *C. elegans* mutants may be obtained from the *C. elegans* mutant collection at the *C. elegans* Genetic Center, University of Minnesota. Alternatively, specific mutants may be generated by standard methods known in the art. Suitable methods are described by J. Sutton and J. Hodgkin in "The Nematode *Caenorhabditis elegans*", Ed. by William B. Wood and the Community of *C. elegans* Researchers CSHL, 1988 594-595; Zwaal et al, "Target - Selected Gene Inactivation in *Caenorhabditis elegans* by using a Frozen Transposon Insertion Mutant Bank" 1993, Proc. Natl. Acad. Sci. USA 90 pp 7431 -7435. A population of nematodes can be subjected to random mutagenesis by using EMS, TMP-UV or radiation (Methods in Cell Biology, Vol 48, ibid). Several selection rounds of PCR may then be performed to select a mutant with a deletion in a desired gene.

In a preferred embodiment, the screening methods may be carried out using a constitutive pharynx pumping strain of *C. elegans*.

Phenotypic, behavioural or biochemical indicators of the activity of the endogenous nematode SERCA protein which can be used as the basis of the screening method include pharynx pumping efficiency, egg laying behaviour, mating behaviour, defecation behaviour, growth rate, movement behaviour, life/death of the nematode and intracellular Ca^{2+} concentration. The methods described above for the measurement of these characteristics are equally applicable to this second aspect of the invention.

In a third aspect the invention provides a method of identifying compounds having pesticidal activity which is carried out in cultured cells as opposed to

whole organisms. This method comprises steps of:

providing cultured cells expressing a SERCA protein; and

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the cells in the presence or absence of test compounds;

wherein a reduction in SERCA activity in the presence of a compound is taken as an indication that the compound has pesticidal activity.

According to this aspect of the invention there is also provided a method of identifying compounds capable of down-regulating the activity of a sarco/endoplasmic reticulum calcium ATPase, which method comprises:

providing cultured cells expressing a SERCA protein;

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the cells in the presence or absence of test compounds; and

thereby identifying compounds capable of down-regulating the activity of SERCA.

These screening methods may be collectively referred to hereinafter as the "cell culture" assays.

In one embodiment of the cell culture assays, the cultured cells may be cells derived from a pest species which express the endogenous pest SERCA protein. This may be a cultured primary cell line or a continuous, transformed cell line. The cell line will be capable of growth in culture, preferably monolayer or suspension culture. Various examples of suitable cell lines derived from pest species are known in the art. Many of these are derived from insect species, for example *Heliothis virescens* (Lynn, Development and characterisation of insect cell lines, Cytotechnology, 20: 3-11, 1996). Methods of culturing

insect cell lines are well known in the art and described, for example, by Maramorosch and McIntosh, Arthropod cell culture systems, 1994, ISBN:0849376424, and Lynn & Shapiro, New cell lines from Heliothis virescens: Characterization and susceptibility to baculoviruses, 1998, 72: 276-280.

The use of cell lines derived from a pest species allows screening on the endogenous pest SERCA protein expressed in the cell line. In further embodiments, the cell culture assays may be based on the use of cultured cells which have been engineered to express a pest SERCA protein. In particular, the assays may be carried out using eukaryotic host cells containing an expression vector comprising nucleic acid encoding the pest SERCA protein.

Suitable expression vectors will include a sequence of deoxynucleotides encoding the pest SERCA protein, including a start codon (usually AUG) and a termination codon for detachment of the ribosome, and also regulatory elements required for expression of the encoded SERCA protein in a eukaryotic host cell. Such regulatory elements may include a promoter region, preferably one which is recognised by RNA polymerase II, optionally one or more additional transcriptional regulatory elements (e.g. enhancer elements) and also a terminator sequence and downstream polyadenylation signal. The vector may also possess an origin of replication allowing replication in prokaryotic cells and one or more selectable markers, such as a gene for antibiotic resistance. A wide range of suitable expression vectors into which nucleic acid encoding the pest SERCA protein may be inserted are available commercially. The expression vector will preferably be a plasmid vector, although virus and phage-based vectors designed for protein expression in eukaryotic host cells may also be used.

The eukaryotic host cells may be a cell line capable of growing in monolayer or suspension culture and will preferably not express high levels of an endogenous SERCA protein (i.e. the SERCA protein encoded in the genome of the host cell). Fibroblast cell lines or epithelial cell lines are most preferred. Suitable cell lines include COS1, BHK21, L929, PC12, CV1, SWISS3T3, HT144, IMR32, HEPG2, MDCK, MCF7, HEK293, Hela, A549, SW48 and G361. However, this list is not exhaustive.

Methods of transfecting expression vectors into eukaryotic host cells are well known in the art (see 'Current Protocols in Molecular Biology', Ed Ausubel et al., John Wiley & Sons, Inc). Most preferably the host cell will be stably or permanently transfected with the expression vector such that it is retained through many cell divisions. However, it is also within the scope of the invention to use cells which are transiently transfected with the expression vector.

As with the nematode-based screening methods, the cell culture assays rely on detection of an indicator of SERCA activity in the presence or absence of a test compound. Suitable indicators of SERCA activity in cultured cells include intracellular Ca^{2+} levels, in particular Ca^{2+} levels in the endoplasmic reticulum, and cell death or apoptosis.

Suitable methods for the measurement of intracellular Ca^{2+} levels in cultured cells are based on fluorescent calcium indicators excited by ultraviolet light, such as fura-2, indo-2,quin-2 or visible light such as fluo-3 and rhod-2 that are available from Molecular Probes, Eugene, USA. The acetoxymethyl esters can passively diffuse across cell membranes to avoid the use of invasive loading techniques. Once inside the cells, these esters are cleaved by intracellular esterases to yield

cell-impermeant fluorescent calcium indicators.

These indicators can be used to perform screens in a high throughput set-up. The test compound is usually added directly prior to the fluorescent indicator, but the screen can also be performed by pre-incubating the cells with the test compound for an incubation time of, for example, 1 min, 5 min, 10 min or 30 min. Fluorescence can be measured directly after the addition of the indicator, but it is preferred to take fluorescence measurements over a period of time, for example every 10 minutes for one hour. Fluorescence data from typical experiments show that measurements after 10 to 15 minutes are generally sufficient to determine the calcium levels in the cell.

Quantitative determination of Ca^{2+} levels in the endoplasmic reticulum of cultured eukaryotic cells can be carried out using the bioluminescent calcium indicator aequorin, or the recombinant form apoaequorin, available from Molecular Probes, Eugene, OR, USA. To target aequorin to specific organelles such as the cytoplasm or endoplasmic reticulum, cultured cell lines may be transiently or stably transfected with an aequorin expression vector containing the aequorin structural gene. Once cells have been transfected with aequorin, they are incubated in a medium containing the cell-permeant coelenterazine or one of its analogs that are available from Molecular Probes, Eugene, USA in order to reconstitute the aequorin complex. After formation of the active aequorin complex, intracellular Ca^{2+} levels are measured by assaying cells for light production using a luminometer.

Screens based on the use of aequorin may be performed in multiwell plates. The test compound can be added prior to the addition of the aequorin substrate, but can also be added in time intervals

before or after the addition of the substrate. Luminescence can be measured directly after the addition of the substrate, but preferentially luminescence measurements are performed over time ranges every 10 minutes for one hour after addition of the substrate. Luminescence data from typical experiments show that measurements after 10 to 15 minutes are sufficient to determine Ca^{2+} levels in the endoplasmic reticulum.

Yet another method for measuring intracellular Ca^{2+} levels is by use of green fluorescent based calcium indicator "cameleon". This method is described by Tsien et al, WO98/40477. The cameleon calcium indicator can be transiently or stably expressed in mammalian, plant, insect or other pest cell lines and fluorescence ratio imaging of cameleon allows time-dependent measurements of intracellular calcium levels (Allen GJ et al., 1999. Cameleon calcium indicator reports cytoplasmic calcium dynamics in Arabidopsis guard cells. Plant J., 19:735-47). Cameleon fluorescence can be measured directly after the addition of the test compound or fluorescence measurements can be taken at various time intervals after addition of the test compound.

The cell culture assays may also be based on the use of cell death or apoptosis as an indicator of SERCA activity in the cell. Methods to determine cell death are well described by Barile Frank in Introduction to in vitro cytotoxicology: mechanisms and methods.1994. ISBN 0849386594. Most of the methods described therein can be performed using standard kits which are commercially available, for example from Molecular Probes or Boehringer Mannheim. Inhibition of SERCA activity leads to apoptosis which can easily measured using specific apoptotic labels as has been described by Smits et al. in WO 99/64586.

A variation on the cell culture assay may be

based on measurement of calcium levels in isolated microsomes rather than intact cultured cells. Techniques for isolation of microsomes are known to those skilled in the art. Isolated microsomes are placed in a solution containing radioactively labelled calcium and ATP. After 10 minutes incubation the amount of radioactivity inside the microsomes is measured in a beta-counter. This approach has been described by Dode, L. *et al.*, 1998. Structure of the human sarco/endoplasmic reticulum Ca^{2+}-ATPase 3 gene. Promoter analysis and alternative splicing of the SERCA3 pre-mRNA. J.Biol.Chem. 273: 13982-13994. Once again the test compound can be added at several time intervals after the isolation of the microsomes, and prior or after the addition of the radioactive calcium.

The cell culture assays will preferably be carried out in multi-well plates of the type well known in the art for use in mid-to-high-throughput screening. In the case of cells engineered to express the pest SERCA protein, non-transfected host cells may also be exposed to the test compounds in order to control for expression of the endogenous host SERCA protein, i.e. to determine the selectivity of the assay for the pest SERCA protein. The non-transfected control cells may also be used to assess general toxicity of the test compounds.

The precise concentration of the candidate compound to be tested in the screening method may vary according to the nature of the compound and such factors as solubility etc. An initial test may be performed using a single concentration of 10 µM. Interesting compounds may then be re-tested to establish a dose-response curve, for example using concentrations of 300 µM, 100 µM, 30 µM, 10 µM, 3 µM, 1 µM, 0.3 µM, 0.01 µM and 0.003 µM and a zero concentration negative control. In general, a dose-

response curve with concentrations between 300 μM and 0.001 μM is sufficient.

The above-described screening methods of the invention, both the nematode-based assays and the cell culture assays, may all be used to identify compounds which have pesticidal activity because of their ability to down-regulate the activity of SERCA proteins, particularly SERCA proteins derived from pest species. Included within the category of 'compounds which down-regulate SERCA activity' may be compounds which act directly on the SERCA protein, including SERCA inhibitors and antagonists. The screens may also identify compounds which act indirectly to down-regulate SERCA activity, for example by affecting regulation of SERCA activity or expression of the SERCA protein. In addition, the screens may also identify compounds that modulate the activity of other proteins in the SERCA pathway, such as proteins involved in the calcium homeostasis of the cell.

There is no limitation on the types of candidate compounds to be tested in the screening methods of the invention. Test compounds may include compounds having a known pharmacological or biochemical activity, compounds having no such identified activity and completely new molecules or libraries of molecules such as might be generated by combinatorial chemistry. Compounds which are DNA, RNA, PNA, polypeptides or proteins are not excluded.

Compounds identified as having pesticidal activity using the nematode-based assay, particularly the assays which do not involve a target pest SERCA protein, may be re-tested in a cell culture assay, for example to assess toxicity of the compound or to assess the specificity of the compound for a pest SERCA protein.

The invention further provides compounds

identified as having the potential to kill pests using the methods of the invention. Such compounds are potential pesticides or can be considered as lead compounds for the development of novel pesticides, including insecticides, herbicides, nematocides and rodenticides. Furthermore, compounds identified as having pesticidal activity against parasitic pest species using the screening methods described herein may have potential utility as anti-parasitic agents or as lead compounds in the development of anti-parasitic agents useful in the treatment of parasitic infections in humans and animals.

The invention will be further understood with reference to the following experimental Examples, together with the accompanying Figures in which:

Figure 1 is an alignment of SERCA cDNA sequences from plant species, indicating consensus sequences and primer locations.

Figure 2 is a general alignment of SERCA cDNA sequences, indicating consensus sequences and primer locations.

Figure 3 shows the complete nucleotide sequence of a plasmid construct comprising the *Arabidopsis* SERCA cDNA in the vector pcDNA3.

Figure 4 shows the complete nucleotide sequence of a plasmid construct comprising the *Heliothis* SERCA cDNA in the vector pcDNA3.

Figure 5 shows the complete nucleotide sequence of a plasmid construct comprising the *Heliothis* SERCA cDNA cloned in the vector pDW2600

(containing the *sca-1* promoter).

Figure 6 shows the complete nucleotide sequence of a plasmid construct comprising the *Arabidopsis* SERCA cDNA cloned in the vector pDW2600 (containing the *sca-1* promoter).

Figure 7 shows the complete nucleotide sequence of the plasmid pDW2700.

Figure 8 shows the complete nucleotide sequence of the plasmid pDW2800.

Figure 9 shows the complete nucleotide sequence of the plasmid pDW2400.

Figure 10 shows the complete nucleotide sequence of the plasmid pDW2422.

Figure 11 shows the complete nucleotide sequence of the plasmid pDW2721, comprising DNA encoding GFP cloned into pDW2700.

Figure 12 illustrates the nucleotide sequence of the genomic fragment of *C. elegans* SERCA bounded by primers SERCA P4 and SERCA P8. Exon IV and exon V are shown in capitals, intron IV in lower case. The fragment deleted in *ok190* is underlined.

Figure 13 shows the nucleic acid sequence of a 732bp EcoRI-HindII fragment of *C. elegans* SERCA exon 5. This fragment was cloned into pGEM3 for use in RNA inhibition experiments.

Figure 14 shows the nucleic acid sequence of a 11207bp SpeI-MluI fragment of cosmid K11D9. This fragment contains the complete *C. elegans* SERCA gene with 5631bp of upstream sequence, the entire coding region and 1088bp of downstream sequence. The fragment was cloned into pUC18 to give plasmid pGK7.

Figure 15 shows the nucleic acid sequence of a 5026 bp fragment of the upstream region of *C. elegans* SERCA, up to and including A of the initiating ATG.

Figure 16 shows the nucleic acid sequence of a 2915bp fragment of the upstream region of *C. elegans* SERCA, as found in plasmid pGK13.

Figure 17 shows the nucleic acid sequence of a 6612bp fragment of the *C. elegans* SERCA gene containing 5637bp of upstream sequence and ending in exon 4.

Figure 18 shows the nucleic acid sequence of the long isoform of the *C. elegans* SERCA cDNA.

Figure 19 shows the nucleic acid sequence of the *C. elegans myo-2* promoter.

Figure 20 shows the nucleic acid sequence of the *C. elegans myo-3* promoter.

Figure 21 shows the nucleic acid sequence of the *C. elegans* vulval muscle enhancer. This is an enhancer element from *ceh-24* that directs gene expression in the vulval muscles (Harfe and Fire, 1998, Developmental 125: 421-429)

Figure 22 shows a dose-response curve for thapsigargin produced using a liquid culture assay.

Figure 23 shows a dose response curve for thapsigargin produced using a plate assay.

Examples

General Methodology

Molecular biology work, such as cloning, PCR etc may be performed as described by Sambrook et al. Molecular cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press or Ausubel et al. Current Protocols in Molecular Biology, John Wiley & Sons, Inc or using minor modifications of the methods described therein.

Manipulations of *C. elegans* worms may be performed using techniques described in Methods in Cell Biology, vol 84; Caenorhabditis elegans: modern biological analysis of an organism, ed. Epstein and Shakes, Academic Press, 1995, or using minor modifications of the methods described therein.

Example 2 Cloning and Expression:

Vectors

pDW2700 general cloning vector containing *C. elegans myo-2* promoter (Figure 7).

pDW2800 general cloning vector containing *C. elegans myo-3* promoter (Figure 8).

pDW2400 general cloning vector containing *C. elegans egl-15* promoter (Figure 9).

pDW2422 general cloning vector containing *C. elegans* *ceh-24* promoter (Figure 10).

pDW2721 cloning vector comprising DNA encoding GFP cloned into in pDW2700.

Cloning of pest SERCA cDNAs

A number of pest SERCA cDNA sequences are available in databases such as GenBank. Further sequences can be cloned using standard PCR technology. Pest SERCA cDNAs can be cloned into standard expression vectors to enable expression in *C. elegans* or in cultured mammalian cells. By way of example, the complete nucleotide sequences of plasmids that enable the expression of *Heliothis* insect SERCA and *Arabidopsis* plant SERCA in *C. elegans* are shown in the accompanying Figures. These plasmids contain SERCA-encoding DNA cloned under the control of the *C.elegans* SERCA (*sca-1*) promoter. The complete nucleotide sequences of plasmid constructs comprising the *Heliothis* SERCA cDNA and the *Arabidopsis* SERCA cDNA in the vector pcDNA3 are also shown.

Primers for cloning *Arabidopsis* and *Heliothis* SERCA in pcDNA3:

Arabidopsis SERCA

Forward primer:cgatggatccatggaagacgcctacgccag
Reverse primer:CGATGGGCCCCTACTTGTCACGCCGGTCC

Heliothis SERCA

Forward primer:cgatggatccatggaggacgctcactcgaaatc
Reverse primer:CGTAGGGCCCTTACAGCTTCCACGTCGGCTG

Strategy for cloning novel pest SERCA cDNAs

1. Assemble multiple alignment of known pest SERCA protein sequences with ClustalW,
2. Make Blocks using program accessible at http://blocks.fhcrc.org/blockmkr/,
3. Design primers using CODEHOP (Rose, et al. (NAR 26: 1628-1635),
4. Select primers from conserved regions,
5. PCR on pest cDNA using appropriate primer combinations ,
6. Clone PCR fragments into appropriate cloning vector,
7. Isolate full length cDNA sequence, for example using 3' or 5' RACE or by hybridisation techniques, e.g. cDNA library screening, using labelled cDNA fragments as probes.

Construction of chimeric SERCA proteins

The introduction of pest SERCA into *C. elegans*, the latter being a SERCA mutant such as *ok190* or a wild-type strain where the endogenous SERCA is inhibited, for example by RNAi technology, will result in rescue of the mutant phenotypes, but maybe not to the full extent. This could be due, for example, to different kinetic properties of the *C. elegans* and pest SERCA proteins. Using chimeric fusion proteins will overcome this problem. A fusion protein may be constructed that has sufficient properties of the *C. elegans* SERCA for rescue of the mutant phenotype, and has those pest SERCA properties sufficient in a screen to select for compounds that alter the pest SERCA activity.

At least four types of fusion proteins are contemplated:

1) A fusion protein harboring the - terminal end of the *C. elegans* SERCA and the C-terminal part of a pest

SERCA.

2) A fusion protein harboring the N-terminal part of a pest SERCA and the C-terminal part of the *C. elegans* SERCA.

3) A fusion protein harboring the C- and - terminal part of the *C. elegans* SERCA and an internal part of a pest SERCA.

4) A fusion protein harboring the C- and - terminal part of a pest SERCA and an internal part of the *C. elegans* SERCA.

Such fusion proteins can easily be constructed using standard molecular biology techniques.

<u>Example 3</u> <u>RNAi:</u>

<u>General strategy</u>

Although primary RNAi experiments indicate that the level of expression the SERCA protein needs to be fine-tuned for the survival of the *C. elegans* nematode, strains in which the level of SERCA activity is reduced, in particular strains in which SERCA activity is reduced in a single tissue, are probably still viable. Due to the sensitivity of *C. elegans* to the level of SERCA activity this could result in a recognisable phenotype, such as reduced pharyngeal pumping, vulva muscle defects, and hence egg laying defects, anal repressor and anal sphincter defects, and hence defecation defects, and body wall muscle defects, and hence movement defects. The phenotypic defects in such strains can be complemented by expression of a pest SERCA protein in the appropriate tissues in order to restore SERCA function to substantially wild-type.

The expression levels of SERCA in *C. elegans* can be specifically reduced by using antisense technology or double stranded RNA inhibition. The use of

antisense technology to specifically reduce expression of a given protein is well known. For the expression of antisense RNA in the worm, the non-coding strand of a fragment of the *sca-1* gene can be expressed under the control of the *sca-1*, myo-2 or myo-3 promoter or any other promoter. The expression of the antisense SERCA RNA will result in the inhibition of expression of SERCA.

Antisense technology can be used to control gene expression through triple-helix formation of antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5′ coding portion or the mature protein sequence, which encodes for the SERCA protein, is used to design an antisense RNA oligonucleotide of from 10 to 50 base pairs in length. The antisense RNA oligonucleotide hybridises to the mRNA *in vivo* and blocks translation of an mRNA molecule into the protein (Okano, J. Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple-helix - see Lee *et al.* Nucl. Acids Res., 6:3073 (1979); Cooney *et al.*, Science, 241:456 (1988); and Dervan *et al.*, Science, 251: 1360 (1991), thereby preventing transcription and the production of the protein.

In order to perform an antisense experiment in C. elegans, an EcoRI-Hind III fragment of SERCA exon 5 was cloned antisense under the control of the *myo-2* promoter, the *myo-3* promoter, the SERCA promoter or the *ceh-24* enhancer and injected into C. elegans. These vectors result in the expression of an antisense SERCA RNA, and hence in inhibition of SERCA activity.

As an alternative to the antisense approach, the expression of a given gene in a cell can also be

specifically reduced by introducing into the cell double stranded RNA corresponding to a region of the transcript transcribed from the gene. Double stranded RNA can be prepared by cloning an appropriate fragment into a plasmid vector containing opposable promoters. A suitable example is the pGEM® series of vectors from Promega Corporation, Madison, WI, USA, which contain opposable promoters separated by a multiple cloning site. When the plasmid vector is transformed or transfected into a host cell or organism which expresses the appropriate polymerases, RNA will be transcribed from each of the promoters. As the vector contains two promoters oriented in the opposite sense, complementary sense and antisense transcripts will be transcribed which will combine to form double stranded RNA. The injection of double stranded RNA in *C. elegans* has previously been described (Fire et al, Potent and Specific Genetic Interference by Double-Stranded RNA in C. elegans 1998, Nature <u>391</u>, 860-811).

<u>Inhibition of expression of *C. elegans* SERCA (sca-1) using RNAi.</u>

732 bp EcoRI-HindIII fragment from *C. elegans* SERCA exon 5 (SEQ ID NO: 1) was PCR amplified and cloned into the vector pGEM3 (PROMEGA corporation, Madison, WI, USA). RNA was in vitro transcribed from both strands using standard procedures. The generated double stranded RNA was injected into *C. elegans* (see Fire at al., 1998, Nature 391:806-811). This resulted in the following phenotypes: 50% of the progeny of the injected animals were embryonic lethal, while the other 50% were early larval lethal. This indicates that SERCA function is vital for *C. elegans*. In conclusion, inhibition of the expression of SERCA in all tissues results in embryonic or early larval lethality of the nematode.

Inhibition of SERCA using RNAi feeding technology

Improved RNAi methods which lead to more stable RNAi phenotypes exist and are described, for example in International patent application No. WO 00/01846. More particularly, an RNAi technology has been developed and tested in which dsRNA can be delivered by feeding the nematode dsRNA or by feeding nematodes with DNA.

pGN4 was constructed by cloning the HindIII - EcoRI fragment of SERCA cloned in vector pGN1 using these same restriction sites. This is the same fragment as was used for *in vitro* transcription and dsRNA injection, described above.

HT115(DE3) bacteria (Fire A, Carnegie Institution, Baltimore, MD) were transfected with pGN4 (and controls with pGN1) and seeded on plates containing IPTG and ampicillin resulting in a high expression of dsRNA by the bacteria. N2 and nuc-1 (e1392) adult nematodes were put on these plates and allowed to lay eggs and the progeny was followed over time. The progeny mostly looked healthy during the larval stages, but the adults (and some of the L4) had a starved appearance (nuc-1 more pronounced then N2). Pharynx pumping was irregular and slower then normal, and the growth rate was somewhat reduced. This example indicates that a stable RNAi phenotype useful in assay development and compound screening can be developed using feeding. As described in co-pending application No. WO 00/01846, other possibilities and variants can be used to create a *C. elegans* SERCA RNAi phenotype. The use of RNAi technology allows the production of *C. elegans* strains in which the activity of the endogenous SERCA protein is abolished/substantially reduced without the construction of a *C. elegans* SERCA mutant.

E. coli HT115 has the following characteristics which make it a useful host cell for high level expression of dsRNA: HT115 (DE3): F- *mcrA mcrb* IN(rrnD-rrnE) 1 λ- *rnc14::tr10* (DE3 lysogen: lacUV5 promoter-T7 polymerase); host for IPTG inducible T7 polymerase expression; RnaseIII-.
Other host strains suitable for expression of dsRNA could be used with equivalent effect.

Example 3 Isolation of SERCA mutants:

Construction of a *C. elegans sca-1* mutant.

The following strategy may be used to isolate a nematode that is mutated in the *sca-1* gene, using standard selection procedures well known in the art.

A population of nematodes are mutagenized, preferentially using UV-TMP, and grown for two generations. The mutagenized worms are distributed per 500 over approximately 1152 plates and grown for an additional two generations. DNA is isolated from a fraction of the worms from each of these plates and used as a template for PCR selection to select for an *sca-1* gene that has a deletion. From a plate with worms, of which some have been demonstrated to contain an *sca-1* deletion, new plates are started with fewer worms. Further rounds of PCR selection finally result in the isolation of a heterozygote *C. elegans* carrying a mutation in the *sca-1* gene (see Jansen et al., 1997, Nature Genetics 17:119-121). As experiments have shown that the expression level of SERCA is important for the survival of the nematode it is possible that this strategy may result only in the isolation of partial knock-out mutations as heterozygote *C. elegans* carrying a severe knock-out mutation in the *sca-1* gene may not viable. In this situation, strategy 1 based

on extrachromosomal expression can be used to isolate severe knock-out mutations.

Analysis of a *C. elegans* mutant (designated *ok190*)

C. elegans strain *ok190* which is mutated in the *sca-1* gene was kindly provided by R. Barstead (Oklahoma, USA). This strain can be purchased from the same supplier or from the *C. elegans* Genetic Center, Minnesota, USA (see above). Heterozygous animals show no defect, but their homozygous progeny die as L1. The lethal phenotype can be rescued by reintroduction of the *C. elegans* gene by injection of pGK7.

Using standard PCR protocols the genomic region of *ok190* around the deleted area was cloned in the following way:

A nested PCR was performed on *C. elegans* genomic DNA using the following primer pairs:

Outer:	SERCA P2:	CGAAGAGCACGAAGATCAGACAG
	SERCA P8:	GAGAGGCGGTTGGTTTGGG
Inner:	SERCA P4:	CCGTTCGTCATCCTTCTCATTC
	SERCA P7:	CGACAGATGGACCGACGAGC

Analysis of the nested PCR product by agarose gel electrophoresis showed that the PCR product in the *ok190* strain harbors a deletion of 1.7 kbp. (The wild-type PCR product from SERCA P4 - SERCA P7 would be 3.4 kbp but the observed *ok190* PCR product was only 1.7 kbp).

To enable detailed analysis of the deleted region the PCR product was cloned into the pCR-XL-TOPO vector (Invitrogen, The Netherlands). The resulting plasmid was designated pKO4. This cloned fragment was then sequenced revealing the exact coordinates of the deleted region. One of the breakpoints of the deletion occurred in the intron between exon IV and

exon V, the other in exon V, deleting a total of 1702 bp of which 1690 bp represent coding sequence.

The nucleotide sequence of the genomic fragment of *C. elegans sca-1* bounded by primers SERCA P4 and SERCA P8 is shown in Figure 12. Exon IV and exon V are shown in capitals, intron IV in lower case. The fragment deleted in *ok190* is underlined.

Example 4 Construction of *C. elegans* strains for use in screening:

Rescue of an *sca-1* mutant *C. elegans* using a pest SERCA cDNA

The following strategy may be used to introduce a pest SERCA transgene onto an *sca-1*(ok190) mutant genetic background in *C. elegans*.

The starting *C. elegans* strain is an *sca-1*(ok190)/qC1 heterozygotic strain. The heterozygous strain is used as an ok190/qC1 strain is viable, whilst both ok190/ok190 and qC1/qC1 are lethal. The qC1 allele is a balancer, and is well known in the area of *C.elegans* genetics.

The following constructs are required:

a) DNA encoding heterologous pest SERCA or heterologous pest /*C. elegans* SERCA chimera under control of the *C. elegans* SERCA promoter (*sca-1* promoter). Other more general promoters able to drive expression of SERCA could be used with equivalent effect.

b) Marker cassette eg. pDW2721 (GFP) or rol-6. For the GFP marker cassette the *myo-2* promoter is chosen to prevent interference with the read out in the pharynx

pumping assay. Using this promoter GFP is only expressed in the pharynx.

The pest SERCA and marker cassettes are transformed into the worm using standard *C. elegans* techniques.

Development:
Rescue the SERCA mutant phenotype of *sca-1*(ok190)/qC1 with heterologous SERCA. Select for wild type phenotype combined with stable fluorescent or roller phenotype (depending on the chosed marker).

Screening:
Rescue of the *sca-1* mutation by expression of a pest SERCA protein results in wild-type phenotypes of pharynx pumping, movement, egg laying, defecation, mating etc. These characteristics can therefore be used as indicators of SERCA activity to perform screens on the pest SERCA target, based on detection of changes in these phenotypes.

C. elegans expressing thapsigargin-resistant pest SERCA

The starting *C. elegans* strain may be wild-type *C.elegans* (N2 strain) or a selected mutant strain.

Required constructs:
a) DNA encoding heterologous pest SERCA or pest SERCA/*C. elegans* SERCA chimera which is resistant to inhibition by thapsigargin under the control of the *C. elegans* SERCA (*sca-1*) promoter.

b) Marker cassette eg. pDW2721 (GFP) or rol-6.

Development:
The expression of a pest SERCA or pest SERCA/*C. elegans* SERCA chimera which is resistant to inhibition by thapsigargin results in rescue of the lethal phenotype induced by lethal doses of thapsigargin.

Screening:
The screen is performed in the presence of a lethal dose of thapsigargin. In the presence of thapsigargin the strain exhibits substantially wild-type pharynx pumping, movement, egg laying, defecation, mating etc. These characteristics can therefore be used as indicators of SERCA activity to perform screens on the pest SERCA target, based on detection of changes in these phenotypes.

<u>*C. elegans* expressing heterologous pest SERCA in a tissue in which expression of the endogenous *C. elegans* SERCA protein is low or absent.</u>
The starting *C. elegans* strain may be wild-type *C.elegans* (N2 strain) or a selected mutant strain.

Required constructs:
a) DNA encoding heterologous pest SERCA or pest SERCA/*C. elegans* SERCA chimera under the control of the *C. elegans unc-119* promoter or any other neuronal promoter.

Development:
The strain exhibits ectopic expression of a pest SERCA protein or pest SERCA/*C. elegans* SERCA chimera in one or more neurons of *C. elegans*. The phenotype is evaluated and a characteristic selected to form the basis of a screen.

Example 5 **Inhibition of endogenous *C. elegans* SERCA by compounds:**

Several compounds are known to inhibit the function of SERCA, such as cyclopiazonic acid, cyproheptadine, thapsigargin, 2,5-di (tert-butyl)-1,4-benzohydroquinone, 2.4-benzoquinone, and vanadate. Other compounds are known to activate the activity of SERCA, such as diethylether, gingerol, and 1-(3,4-dimethoxyphenyl)-3-dodecanone. Still other compounds have a dual activity, they stimulate SERCA at low concentrations, but inhibit at high concentrations, such as phenothiazines, and pentobarbital.

Using two kinds of assays, the optimal concentration of compounds that inhibit the activity SERCA has been determined. The first assay is designated the drop or plate assay in which the nematodes are fed *E. coli* strains pre-loaded with the compound. In a second assay, the compound is administrated to the worm in liquid culture.

Plate assay

A standard plate drop assay is performed according to the following protocol. 4ml NGM agar (see "The nematode *C. elegans*" Ed. by William B. Wood and the Community of *C. elegans* Researchers, CSHL Press, 1988, pg589) is into 3cm plates and seeded with approximately 5µl of an *E. coli* overnight culture and grown preferably for one week at room temperature. Approximately 10µl of test compound dissolved in DMSO or other suitable solvent is pipetted onto the bacterial lawn so that the lawn is covered completely. After overnight soaking in or compound, one *C. elegans* (L4 stage) per plate is put onto the bacterial lawn. Plates are incubated at 21°C and checked after some

hours. Plates are checked again after 4 days for phenotypes of the F1 progeny (control shows all stages up to gravid hermaphrodites).

Thapsigargin at various concentrations (5 µM, 2.5 µM and 1.25 µM) causes the nematode to stop pharynx pumping within 10 min. Within an hour the worms restart pumping, although at a low level. The worms are pale and thin and have a slow and irregular movement, with an increased amplitude. No plate drop response is observed, and the worms show poor backing, reduced pumping and strong constipation. The worms have a defective gonad with only very few eggs, and a protruding vulva. Some worms also have a protruding rectum. Progeny reaches L2 stage only after four days, and the brood size is very small. Lower concentrations of thapsigargin (0.5 µM, 0.25 µM, 0.125 µM) still cause reduced brood size.

2,5-di-tert butylhydroquinone at a concentration of 500 µM resulted in pale, starved, thin worms with slow movement, defective gonad, constipated and reduced brood size.

Cyclopiazonic acid at a concentration of 500 µM resulted in nematodes that lay still or move slowly after one hour. The worms showed strong avoidance and after 24 hours they look starved, pale and thin, with only a few eggs in the body, a defective gonad, and reduced brood size. A delayed growth of the F1 generation was observed.

Thapsigargicin at 500 µM, 125 µM, 31 µM, 10 µM, 5 µM resulted in nematodes with similar phenotypes to those described above for thapsigargin at 5 µM, 2.5 µM, 1.25 µM. Lower concentrations of thapsigargicin (3 µM and 1.5 µM) caused a slightly reduced brood size.

Thapsigargin-epoxide did not result in a clear observable effect, even at the highest concentration tested (1 mM drop, 5 µM end concentration).

1,4-benzoquinone did not result in a clear

observable effect, even at the highest concentration tested (100 mM drop, 500 μM end concentration).

Liquid culture assay

Thapsigargin at 100, 50 and 20 μM resulted in small worms which show slow and loopy movement. They had a protruding vulva, and no progeny (or no progeny that grows up) were observed. At lower concentrations of 10 μM and 5 μM a reduced number of progeny and delayed growth could be observed.

2,5-di-tert butylhydroquinone at a concentration of 1mM resulted in progeny exhibiting delayed growth and the worms were observed to be thinner than 'normal' worms.

Cyclopiazonic acid at a concentration of 1mM resulted in pale, thin worms with a slow movement and a very strongly reduced brood size. At lower concentrations of 0.5mM, growth delay was observed.

Thapsigargicin at 1000 μM, 250 μM, 62.5 μM and 16 μM concentrations resulted in small worms with slow and loopy movement, a protruding vulva, and no progeny (or no progeny that grows up) were observed. At lower concentrations of 10 μM, delayed growth and reduced progeny were observed.

The effect of thapsigargin on progeny of wild-type strains was tested with the liquid assay: On an average of 12 worms, the number of progeny for the different concentrations is summarized in Figure 22.

The effect of thapsigargin was also tested on progeny of wild-type strains using the plate assay: On an average of 12 worms the number of progeny at different concentrations is summarized in Figure 23.

The effect of thapsigargin on the production of progeny was determined for a number of different *C. elegans* strains. The numbers of progeny produced following thapsigargin treatment was counted for an average of 15 animals, the results are summarised as

follows:

unc-31:	control : 132
	0.5 mM : 35
	1 mM : 5,6
srf-3:	control: 50
	1 mM : 18,3

The effect of thapsigargin on pharynx pumping behaviour was also determined. In wild-type worms, all animals stopped pumping after 10 minutes. In mutant strain unc-31 at a concentration of 1 mM thapsigargin, all worms stopped pumping after 10 minutes, some start again after half an hour, but pumping is only one third of normal speed.

In summary, the above experiments demonstrate that inhibition of *C. elegans* SERCA activity using thapsigargin or other chemical inhibitors of SERCA results in worms with recognisable phenotypic characteristics, including reduced growth, reduced rate of pharynx pumping and reduced numbers of progeny. These phenotypic changes can be used as the basis of a screen for other compounds which inhibit the activity of the endogenous *C. elegans* SERCA protein.

Example 7 *C. elegans* screening technology:

Distribution of nematodes, and dilution of compounds.

The following is a basic protocol for performing a compound screen in 96 well plates.

Preferentially, synchronized worms are used. The production of large amounts of synchronized worms has been described in (Methods in cell biology, Vol. 48, ibid). After the worms have grown to the preferred stage, they are washed in M9 buffer prior to further use, and re-suspended in an assay buffer (40mM NaCl,

6mM Kcl, 1mM $CaCl_2$, 1mM $MgCl_2$). (10 X M9 buffer: 30g KH_2PO_4, 60 g Na_2HPO_4, 50 g NaCl, 10 ml MgS04 1M, made up to 1 litre with H_2O). Other buffers than M9 buffer can be suitable for this purpose.

The worms are then diluted and resuspended in semi-soft agar (final concentration of 0.25% low melting agarose in M9 buffer). This procedure results in an equal, homogenous and stabilised suspension of the nematodes. Other polymers than low melting agarose can be used in this procedure. The presence of a homogenous worm suspension facilitates the equal distribution of the worms in the multi-well plates, but is not essential. Any other method that results in a homogenous distribution of the nematodes worms over the wells will be useful. More specifically, the use of a worm dispenser will result in even a better, and hence a more equal distribution of the worms over the wells of the multi-well plate.

The worms are distributed in the multi-well plates using electronic 8 channel pipettes. In a preferred set-up of this experiment 40 +/- 5 worms are added to every well of the microtiter plate.

Compounds are dissolved in DMSO. Any other solvent can be used for this purpose, but most selected compounds appear to be soluble in DMSO. The compounds are added in the wells at various concentrations. The concentration of the DMSO should not be too high and preferentially should not exceed 1%, more preferentially the concentration of the DMSO should not exceed 0.5% and even more preferentially, the concentration of the DMSO is lower than 0.3%.

<u>General pharynx pumping assay.</u>

Depending on the specific assay which it is desired to perform, different *C. elegans* strains can be used. Screens to select for compounds inhibiting the pumping rate of the *C. elegans* pharynx are

preferably performed with mutant *C. elegans* strains which have a constitutively pumping pharynx. Wild-type worms can also be used in this screen, but the mutants worms are preferred. Other *C. elegans* mutants can be used in this screen to select for inhibitors of pumping. The selected mutant *C. elegans* with the constitutively pumping pharynx pumps medium into the gut at a constant rate and reduction/rescue of this phenotype can easily be scored, which facilitates the detection and selection of compounds.

The pumping rate of the pharynx is measured indirectly by adding a marker molecule precursor such as calcein-AM to the medium and measuring the formation of marker dye in the *C. elegans* gut. Calcein-AM is cleaved by esterases present in the *C. elegans* gut to release calcein, which is a fluorescent molecule. The pumping rate of the pharynx will determine how much medium will enter the gut of the worm, and hence how much calcein-AM will enter the gut of the worm. Therefore by measuring the accumulation of calcein in the nematode gut, detectable by fluorescence, it is possible to determine the pumping rate of the pharynx.

Compounds that alter the pumping rate of the pharynx will result in more or less uptake of the calcein-AM and hence in more or less fluorescent signal. Moreover, using a multi-well plate reader, the fluorescence can be measured rapidly and quantitatively, resulting in a fast, quantitative high throughput screening method for the identification of compounds with potential pharmacological activity.

To perform the pharynx pumping screen with calcein-AM, a concentration of between 1 and 100μM calcein-AM is added into the medium. Preferably 5 to 10μM calcein-AM is used. Fluorescence is measured using a multi-well plate reader (Victor2, Wallac Oy,

Finland) with following settings: Ex/Em = 485/530.

This measurement of the pharynx pumping rate by detecting the accumulation of a marker molecule is not limited to calcein-AM. Other precursors can be used and thus the assay as described here can be changed to be suitable for other precursors. The precursor can be cleaved by esterases, but could also be a substrate for other enzymes in the nematode gut. Furthermore, the marker molecule should not necessary be a fluorescent molecule, but can be a molecule detectable by other methods. Most of these precursor substances are commercially available or could be synthesized according to methods known in the art. Some examples are:

With a fluorescent read out:
-Esterases substrates: Calcein-AM, FDA, BCECF-AM
-Alkaline phosphatase substrates: Fluorescein diphospate (FDP)

-Endoproteases; Aminopeptidase substrates: CMB-leu

With a luminescent read out:
-alkaline phosphatase substrates: AMPPD

With a colour read out.
-Glucuronidase substrates: X-gluc

Other target enzymes present in the gut for which substrates can be found or developed are DNAses, ATPases, lipases and amylases. An overview of various marker molecules, mainly fluorescent can be found in "Handbook of fluorescent probes and research chemicals, molecular probes, ed. by R. P. Haughland"

Example 8 Inhibition of SERCA in cultured mammalian cells:

COS cells have been transfected with erAEQ/pCDNAi provided by Molecular probes, to investigate the influence of calcium modulation of thapsigargin in these cells. Transfection was performed using the Lipofectamine Plus reagent (Life technloglogies, Inc) according to the standard protocol supplied by the manufacturer. Cell lysis was performed as described in "The Molecular Sampler Kit" provided by Molecular Probes, to determine the best substrate. Experiments show that for COSI cells coelentazine hcp is the best substrate (data not shown). For other cells the most suitable substrate would need to be determined by experiment.

Tests were repeated in multiwell plates, without cell lysis. The transfected cells were treated with thapsigargin and aequorin fluorescence was measured directly. A clear variation was observed between cells treated with thapsigargin and cells that have not been treated. Measurements in a high throughput format can be made from 5 minutes to at least 45 minutes after contacting the cells with the appropriate test compound.

GenBank accession numbers of SERCA cDNAs

Arabidopsis thaliana: Q9SWS8 ,O04987 ,O23087.
Artemia sanfranciscana: ATC_ARTSF.
Aspergillus niger: AAF37300.
Bacillus halodurans: BAB06234.
Bacillus subtilis: O34431.
Bos taurus: AAF64433.
Caenorhabditis elegans: Q9XTG6.
Candida albicans: CAB87245.
Drosophila melanogaster: ATC1_DROME ,Q9VNR2.
Dunaliella bioculata: ATC1_DUNBI.

Gallus gallus: Q9YGL9 ,ATC1_CHICK, B40812.
Heliothis virescens: O96696.
Homo sapiens: O60900 ,ATC1_HUMAN.
Leishmania mexicana: O09489.
Lycopersicon esculentum: Q42883.
Makaira nigricans: ATC1_MAKNI.
Methanobacterium thermoautotrophicum: O27560.
Mus musculus: Q64517 ,ATC2_MOUSE.
Mycobacterium tuberculosis: CTPF_MYCTU.
Neurospora crassa: Q9UUY0.
Oryctolagus cuniculus: ATC2_RABIT.
Oryza sativa: BAA90510 ,O04938.
Paramecium tetraurelia: CAB96170 ,O61073.
Patinopecten yessoensis: O96039.
Placopecten magellanicus: O77070.
Plasmodium berghei: Q27764.
Plasmodium falciparum: ATC_PLAFK.
Procambarus clarkii: O17314.
Pseudomonas aeruginos: AE004572_6.
Rana esculenta: ATC1_RANES.
Schistosoma mansoni: O96527 ,Q27779.
Schizosaccharomyces pombe: O59868.
Synechococcus sp.: ATCL_SYNP7.
Synechocystis sp.: Q59999.
Synechocystis sp: SSPMA1_1.
Trichomonas vaginalis: Q95060.
Trypanosoma brucei: ATC_TRYBB.
Trypanosoma cruzi: O96608.
Ureaplasma urealyticu: AE002123_6.
Zea mays: AAF73985.

LIST OF PEST SPECIES:

ID	EnglishText	LatinText	FamilyOrderText	LatinTextOneWord
1	Amaranths	Amaranthus spp.	Amaranthaceae	Amaranthus
2	American bollworm	Helicoverpa zea	Lepidoptera: Noctuidae	Helicoverpa
3	American cockroach	Periplaneta americana	Dictyoptera: Blattidae	Periplaneta
4	American serpentine leaf miner	Liriomyza trifolii	Diptera: Agromyzidae	Liriomyza
5	Angoumois grain moth	Sitotroga cerealella	Lepidoptera: Gelechiidae	Sitotroga
6	Angular leaf spot, cucurbits	Pseudomonas lachrymans	Eubacteriales	Pseudomonas
7	Annual ryegrass	Lolium rigidum	Gramineae	Lolium
8	Anopheles mosquitos	Anopheles spp.	Diptera: Culicidae	Anopheles
9	Anthracnose, french beans	Colletotrichum lindemuthianum	Melanconiales	Colletotrichum
10	Anthracnose, various root rot and leaf	Colletotrichum spp.	Melanconiales	Colletotrichum
11	Ants	Formicidae	Hymenoptera	Formicidae
12	Aphid parasitoid wasps	Aphidius spp.	Hymenoptera:	Aphidius
13	Apple blossom weevil	Anthonomus pomorum	Coleoptera:	Anthonomus
14	Apple leaf miner	Phyllonorycter blancardella	Lepidoptera:	Phyllonorycter
15	Apple leaf miner	Lyonetia clerkella	Lepidoptera: Lyonetiidae	Lyonetia
16	Argentine ant	Iridomyrmex humilis	Hymenoptera:	Iridomyrmex
17	Army worms	Spodoptera spp.	Lepidoptera: Noctuidae	Spodoptera
18	Arrowhead	Sagittaria sagittifolia	Alismataceae	Sagittaria
19	Australian bush fly	Musca vetustissima	Diptera: Muscidae	Musca
20	Australian sheep blowfly	Lucilia cuprina	Diptera: Calliphoridae	Lucilia
21	Bacteral canker, prunus	Pseudomonas mors-prunorum	Eubacteriales	Pseudomonas
22	Bacterial blights and leaf spots,	Pseudomonas spp.	Eubacteriales	Pseudomonas
23	Bacterial grain rot, rice	Pseudomonas glumae	Eubacteriales	Pseudomonas
24	Bacterial leaf spots, various hosts	Xanthomonas spp.	Eubacteriales	Xanthomonas
25	Bacterial rot, celery	Erwinia carotovora	Eubacteriales	Erwinia
26	Bacteriosis, cotton	Xanthomonas malvacearum	Eubacteriales	Xanthomonas
27	Banana black heart	Gibberella fujikuroi	Hypocreales	Gibberella
28	Banana leaf spot, sigatoka	Mycosphaerella musicola	Dothidiales	Mycosphaerella
29	Banana root borer	Cosmopolites sordidus	Coleoptera:	Cosmopolites
30	Banana weevil	Cosmopolites sordidus	Coleoptera:	Cosmopolites
31	Bandicoot rats	Bandicota spp.	Rotentia: Muridae	Bandicota
32	Barnyard grass	Echinochloa crus-galli	Gramineae	Echinochloa
33	Barnyard grass, awnless	Echinochloa colonum	Gramineae	Echinochloa
34	Barren brome	Bromus sterilis	Gramineae	Bromus
35	Basal stem rot, cucurbits	Erwinia carotovora	Eubacteriales	Erwinia
36	Bean beetles	Epilachna spp.	Coleoptera:	Epilachna
37	Bean weevils	Sitona spp.	Coleoptera:	Sitona
38	Bearded oat	Avena barbata	Gramineae	Avena
39	Bed bug	Cimex lectularius	Heteroptera: Cimicidae	Cimex
40	Beet army worm	Spodoptera exigua	Lepidoptera: Noctuidae	Spodoptera
41	Beet cyst nematode	Heterodera schachtii	Nematoda:	Heterodera
43	Beet leaf weevil	Tanymecus pallidus	Coleoptera:	Tanymecus
42	Beet leaf-miner	Pegomya hyoscamni	Diptera: Anthomyiidae	Pegomya
44	Begonia	Begonia elatior	Begoniaceae	Begonia
45	Bermuda grass	Cynodon dactylon	Gramineae	Cynodon

46	Bindweed, large	Calystegia sepium ssp. sepium	Convolvulaceae	Calystegia
47	Bird skin mites	Cnemidocoptes spp.	Acari: Sarcoptidae	Cnemidocoptes
48	Biting midges	Ceratopogonidae	Diptera	Ceratopogonidae
49	Black bean aphid	Aphis fabae	Homoptera: Aphididae	Aphis
50	Black bent	Agrostis gigantea	Gramineae	Agrostis
51	Black bindweed	Fallopia convolvulus	Polygonaceae	Fallopia
52	Black flies	Simulium spp.	Diptera: Simuliidae	Simulium
54	Black leaf streak, banana	Mycosphaerella fijiensis	Dothidiales	Mycosphaerella
55	Black mould	Cladosporium spp.	Hyphales	Cladosporium
56	Black nightshade	Solanum nigrum	Solanaceae	Solanum
57	Black olive scale	Saissetia oleae	Homoptera: Coccidae	Saissetia
58	Black rat	Rattus rattus	Rotentia: Muridae	Rattus
59	Black root rot, tobacco	Thielaviopsis spp.	Deuteromycotina	Thielaviopsis
60	Black rot, apple	Botryosphaeria obtusa (=	Dothidiales	Botryosphaeria
61	Black rot, grapevines	Guignardia bidwellii	Dothidiales	Guignardia
62	Black stem rust, grasses	Puccinia graminis	Uredinales	Puccinia
53	Black-grass	Alopecurus myosuroides	Gramineae	Alopecurus
63	Blackcurrant gall-mite	Cecidophyopsis ribis	Acari: Eriophyidae	Cecidophyopsis
64	Blackcurrant rust	Cronartium ribicola	Uredinales	Cronartium
65	Blackleg, beet crops	Aphanomyces cochlioides	Saprolegniales	Aphanomyces
66	Blackleg, potatoes	Erwinia carotovora	Eubacteriales	Erwinia
67	Blackspot, roses	Diplocarpon rosae	Helotiales	Diplocarpon
68	Bladderworts	Utricularia spp.	Lentibulariaceae	Utricularia
69	Blast, rice	Pyricularia oryzae	Hyphales	Pyricularia
70	Blight, capsicums	Phytophthora capsici	Peronosporales	Phytophthora
71	Blight, potato	Phytophthora infestans	Peronosporales	Phytophthora
72	Blight, tomato	Phytophthora infestans	Peronosporales	Phytophthora
73	Blister blight, tea	Exobasidium vexans	Exobasidiales	Exobasidium
74	Blossom or pollen beetles	Meligethes spp.	Coleoptera: Nitidulidae	Meligethes
75	Blossom wilt, apple, plum	Sclerotinia laxa	Helotiales	Sclerotinia
76	Blue cattle louse	Solenopotes capillatus	Phthiraptera:	Solenopotes
77	Blue mould, citrus	Penicillium italicum	Hyphales	Penicillium
78	Blue mould, tobacco	Peronospora tabacina (=	Peronosporales	Peronospora
79	Boll weevil	Anthonomus grandis	Coleoptera:	Anthonomus
80	Booklice	Psocoptera	Insecta	Psocoptera
81	Bracken	Pteridium aquilinum	Filicales	Pteridium
82	Brambles	Rubus spp.	Rosaceae	Rubus
83	Branched bur-reed	Sparganium erectum	Sparganiaceae	Sparganium
84	Brassica cyst nematode	Heterodera cruciferae	Nematoda:	Heterodera
85	Brassica gall and stem weevils	Ceutorhynchus spp.	Coleoptera:	Ceutorhynchus
86	Broad mite	Polyphagotarsonemus latus	Acari: Tarsonemidae	Polyphagotarsonemu
87	Brooks spot, apple	Mycosphaerella pomi	Dothidiales	Mycosphaerella
89	Brown foot rot, cereals	Gibberella spp. (= various	Hypocreales	Gibberella
90	Brown rat	Rattus norvegicus	Rotentia: Muridae	Rattus
91	Brown rot, apple, pear, plum	Sclerotinia fructigena,	Helotiales	Sclerotinia
92	Brown rust, barley	Puccinia hordei	Uredinales	Puccinia
93	Brown rust, chrysanthemum	Puccinia chrysanthemi	Uredinales	Puccinia

94	Brown rust, wheat	Puccinia recondita	Uredinales	Puccinia
95	Brown soft scale	Coccus hesperidum	Homoptera: Coccidae	Coccus
96	Brown spot, peanut	Mycosphaerella arachidis	Dothidiales	Mycosphaerella
97	Brown spot, rice	Cochliobolus miyabeanus	Dothidiales	Cochliobolus
98	Brown stripe, sugar cane	Bipolaris stenospila	Hyphales	Bipolaris
88	Brown-banded cockroach	Supella longipalpa	Dictyoptera: Blattidae	Supella
99	Buffalo fly	Haematobia irritans exigua	Diptera: Muscidae	Haematobia
100	Buffalograss	Brachiaria mutica (= Panicum	Gramineae	Brachiaria
101	Bugs	Heteroptera	Hemiptera	Heteroptera
102	Bulb mites	Rhizoglyphus callae, R. robini	Acari: Acaridae	Rhizoglyphus
103	Bulb scale mite	Steneotarsonemus laticeps	Acari: Tarsonemidae	Steneotarsonemus
104	Bullrushes	Typha spp.	Typhaceae	Typha
105	Bunt, stinking smut	Tilletia caries	Ustilaginales	Tilletia
106	Burrowing nematode	Radopholus similis	Nematoda: Tylenchidae	Radopholus
107	Butt rot, conifers	Heterobasidion annosum	Aphyllophorales	Heterobasidion
108	Buttercups	Ranunculus spp.	Ranunculaceae	Ranunculus
109	Cabbage looper	Trichoplusia ni	Lepidoptera: Noctuidae	Trichoplusia
110	Cabbage root fly	Delia radicum	Diptera: Anthomyiidae	Delia
111	Cabbage seed weevil	Ceutorhynchus assimilis	Coleoptera:	Ceutorhynchus
112	Cabbage stem weevil	Ceutorhynchus quadridens	Coleoptera:	Ceutorhynchus
113	Cabbage white butterflies	Pieris spp.	Lepidoptera: Pieridae	Pieris
114	Californian red scale	Aonidiella aurantii	Homoptera: Diaspididae	Aonidiella
115	Canadian pondweed	Elodea canadensis	Hydrocharitaceae	Elodea
116	Canary grass, awned	Phalaris paradoxa	Gramineae	Phalaris
117	Canary grasses	Phalaris spp.	Gramineae	Phalaris
118	Canker, apple, pear	Nectria galligena	Nectriaceae	Nectria
119	Capsid bugs	Miridae	Heteroptera	Miridae
120	Carmine spider mite	Tetranychus cinnabarinus	Acari: Tetranychidae	Tetranychus
121	Carpenter ants	Camponotus spp.	Hymenoptera:	Camponotus
122	Carpet beetles	Anthrenus spp.	Coleoptera: Dermestidae	Anthrenus
123	Carrot fly	Psila rosae	Diptera: Psilidae	Psila
124	Carrot leaf blight	Alternaria dauci	Hyphales	Alternaria
125	Cat flea	Ctenocephalides felis	Siphonaptera: Pulicidae	Ctenocephalides
126	Cattle biting louse	Bovicola bovis	Phthiraptera:	Bovicola
127	Cattle tail louse	Haematopinus quadripertusus	Phthiraptera:	Haematopinus
128	Cereal leaf beetle	Oulema melanopus	Coleoptera:	Oulema
129	Chamomiles	Anthemis spp.	Compositae	Anthemis
130	Charlock	Sinapis arvensis	Cruciferae	Sinapis
131	Cherry leaf spot	Blumeriella jaapii	Helotiales	Blumeriella
132	Chicken mite	Dermanyssus gallinae	Acari: Dermanyssidae	Dermanyssus
133	Chigoe flea	Tunga penetrans	Siphonaptera: Pulicidae	Tunga
134	Chinch bug	Blissus leucopterus	Lygaeidae	Blissus
135	Chrysanthemum leaf miner	Phytomyza syngenesiae	Diptera: Agromyzidae	Phytomyza
136	Chrysanthemum leaf miner parasitoid	Dacnusa sibirica	Hymenoptera:	Dacnusa
137	Chrysomelid beetles	Chrysomelidae	Coleoptera	Chrysomelidae
138	Cigarette beetle	Lasioderma serricorne	Coleoptera: Anobiidae	Lasioderma
139	Citrus aphid	Aphis citricola	Homoptera: Aphididae	Aphis

140	Citrus canker	Xanthomonas citri	Eubacteriales	Xanthomonas
141	Citrus mealybug	Planococcus citri	Homoptera:	Planococcus
142	Citrus red mite	Panonychus citri	Acari: Tetranychidae	Panonychus
143	Citrus rust mite	Phyllocoptruta oleivora	Acari: Eriophyidae	Phyllocoptruta
144	Cleavers	Galium aparine	Rubiaceae	Galium
145	Click beetles	Elateridae	Coleoptera	Elateridae
146	Clothes moths	Tinea spp.	Lepidoptera: Tineidae	Tinea
147	Clothes moths	Tineola spp.	Lepidoptera: Tineidae	Tineola
148	Clover bryobia mite	Bryobia praetiosa	Acari: Tetranychidae	Bryobia
149	Club-rushes	Scirpus spp.	Cyperaceae	Scirpus
150	Clubroot, brassicas	Plasmodiophora brassicae	Plasmodiophorales	Plasmodiophora
151	Coccomycosis	Blumeriella jaapii	Helotiales	Blumeriella
152	Cockchafer	Melolontha melolontha	Coleoptera: Scarabaeidae	Melolontha
153	Cocklebur	Xanthium pennsylvanicum	Compositae	Xanthium
154	Cockroaches	Blattella spp.	Dictyoptera: Blattidae	Blattella
155	Cockspur, rice	Echinochloa oryzicola (= E.	Gramineae	Echinochloa
156	Cocoa capsid	Sahlbergella singularis	Heteroptera: Miridae	Sahlbergella
157	Cocoa capsid	Distantiella theobroma	Heteroptera: Miridae	Distantiella
158	Codling moth	Cydia pomonella	Lepidoptera: Tortricidae	Cydia
159	Coffee rust	Hemileia vastatrix	Uredinales	Hemileia
160	Collar rot, apple	Phytophthora cactorum	Peronosporales	Phytophthora
161	Colorado beetle	Leptinotarsa decemlineata	Coleoptera:	Leptinotarsa
162	Columbus grass	Sorghum almum	Gramineae	Sorghum
163	Common amaranth	Amaranthus retroflexus	Amaranthaceae	Amaranthus
164	Common chickweed	Stellaria media	Caryophyllaceae	Stellaria
165	Common cockroach	Blatta orientalis	Dictyoptera: Blattidae	Blatta
166	Common couch	Elymus repens	Gramineae	Elymus
167	Common orache	Atriplex patula	Chenopodiaceae	Atriplex
168	Common scab, potato, beet	Streptomyces scabies	Actinomycetales	Streptomyces
169	Confused flour beetle	Tribolium confusum	Coleoptera:	Tribolium
170	Corn marigold	Chrysanthemum segetum	Compositae	Chrysanthemum
171	Corn rootworms	Diabrotica spp.	Coleoptera:	Diabrotica
172	Corn spurrey	Spergula arvensis	Caryophyllaceae	Spergula
173	Cotton boll rot	Gibberella fujikuroi	Hypocreales	Gibberella
174	Cotton leaf perforator	Bucculatrix thurberiella	Lepidoptera: Lyonetiidae	Bucculatrix
175	Cotton leaf worm	Alabama argillacea	Lepidoptera: Noctuidae	Alabama
176	Cotton leafhoppers	Empoasca spp.	Homoptera: Cicadellidae	Empoasca
177	Cotton rat	Sigmodon hispidus	Rodentia: Cricetidae	Sigmodon
178	Crabgrass	Digitaria sanguinalis	Gramineae	Digitaria
179	Crabgrass, tropical	Digitaria adscendens (= D.	Gramineae	Digitaria
180	Crane flies	Tipula spp.	Diptera: Tipulidae	Tipula
181	Crane's bills	Geranium spp.	Geraniaceae	Geranium
182	Creeping bent	Agrostis stolonifera	Gramineae	Agrostis
183	Crickets	Cricetus spp.	Saltatoria: Gryllidae	Cricetus
184	Crown rot, apple	Phytophthora cactorum	Peronosporales	Phytophthora
185	Cutworm	Noctua pronuba	Lepidoptera: Noctuidae	Noctua
186	Cutworms	Agrotis spp., Euxoa spp.,	Lepidoptera: Noctuidae	Agrotis

187	Cyst nematodes	Heteroderidae	Nematoda	Heteroderidae
188	Damping off, various hosts	Pellicularia spp.	Tulasnellales	Pellicularia
189	Damping off, various hosts	Phytophthora spp.	Peronosporales	Phytophthora
190	Damson-hop aphid	Phorodon humuli	Homoptera: Aphididae	Phorodon
191	Dark leaf spot, brassicas	Alternaria brassicae, Alternaria	Hyphales	Alternaria
192	Dart moths	Euxoa spp.	Lepidoptera: Noctuidae	Euxoa
193	Dayflower	Commelina spp.	Commelinaceae	Commelina
194	Dead arm, grape vines	Phomopsis viticola	Sphaeropsidales	Phomopsis
195	Death watch beetle	Xestobium rufovillosum	Coleoptera: Dermestidae	Xestobium
196	Deer flies	Chrysops spp.	Diptera: Tabanidae	Chrysops
197	Diamond-back moth	Plutella xylostella	Lepidoptera:	Plutella
198	Docks and sorrels	Rumex spp.	Polygonaceae	Rumex
199	Dog	Canis familiaris	Carnivora: Canidae	Canis
200	Dog flea	Ctenocephalides canis	Siphonaptera: Pulicidae	Ctenocephalides
201	Dollar spot, turf	Sclerotinia homeocarpa	Helotiales	Sclerotinia
202	Downy mildew, brassicae	Peronospora parasitica	Peronosporales	Peronospora
203	Downy mildew, cereals	Scerophthora macrospora	Peronosporales	Scerophthora
204	Downy mildew, cucurbits	Pseudoperonospora cubensis	Peronosporales	Pseudoperonospora
205	Downy mildew, grapevine	Plasmopara viticola	Peronosporales	Plasmopara
206	Downy mildew, hops	Pseudoperonospora humuli	Peronosporales	Pseudoperonospora
207	Downy mildew, lettuce	Bremia lactucae	Peronosporales	Bremia
208	Downy mildew, sorghum	Peronosclerospora spp.	Peronosporales	Peronosclerospora
209	Downy mildew, wheat	Scerophthora spp.	Peronosporales	Scerophthora
210	Dry bubble, mushrooms	Verticillium fungicola	Hyphales	Verticillium
211	Dry rot	Fusarium coeruleum	Hyphales	Fusarium
212	Dutch-elm disease	Ceratocystis spp.	Microasaceae	Ceratocystis
213	Ear blight, cereals	Gibberella spp. (= various	Hypocreales	Gibberella
214	Ear blights, various hosts (Imperfect	Fusarium spp.	Hyphales	Fusarium
215	Ear-mange mites	Otodectes spp.	Acari: Psoroptidae	Otodectes
216	Earwigs	Dermaptera	Insecta	Dermaptera
217	Egyptian cotton leafworm	Spodoptera littoralis	Lepidoptera: Noctuidae	Spodoptera
218	Elodea, Florida	Hydrilla verticillata	Hydrocharitaceae	Hydrilla
219	Eriophyid mites	Eriophyidae	Acari	Eriophyidae
220	European corn borer	Ostrinia nubilalis	Lepidoptera: Pyralidae	Ostrinia
221	European pine sawfly	Neodiprion sertifer	Hymenoptera:	Neodiprion
222	European vine moth	Lobesia botrana	Lepidoptera: Tortricidae	Lobesia
223	Eye-spot, cereals	Pseudocercosporella	Hyphales	Pseudocercosporella
224	Fairy rings	Marasmius oreades and other	Agaricaceae	Marasmius
225	Fall panicum	Panicum dichotomiflorum	Gramineae	Panicum
226	False oat-grass	Arrhenatherum elatius	Gramineae	Arrhenatherum
227	Fat hen	Chenopodium album	Chenopodiaceae	Chenopodium
228	Field bindweed	Convolvulus arvensis	Convolvulaceae	Convolvulus
229	Field pansy	Viola arvensis	Violaceae	Viola
230	Field rat	Arvicanthis niloticus, Rattus	Rotentia: Muridae	Arvicanthis
231	Field vole	Microtus agrestis	Rotentia: Muridae	Microtus
232	Filamentous bacteria	Actinomycetales		Actinomycetales
233	Flea beetle	Phyllotreta striolata	Coleoptera:	Phyllotreta

234	Flea beetles	Chaetocnema spp., Phyllotreta	Coleoptera:	Chaetocnema
235	Fleas	Pulicidae	Siphonaptera	Pulicidae
236	Flies	Diptera	Insecta	Diptera
237	Florida beggarweed	Desmodium tortuosum	Leguminosae	Desmodium
238	Flour beetles	Cucujidae	Coleoptera	Cucujidae
239	Flour beetles	Tribolium spp.	Coleoptera:	Tribolium
240	Flour mites	Acarus spp.	Acari: Acaridae	Acarus
241	Fly speck disease, apple	Schizothyrium pomi	Dothidiales	Schizothyrium
242	Follicle mites	Demodex spp.	Acari: Demodicidae	Demodex
243	Foot rot, cereals, grasses	Cochliobolus sativus	Dothidiales	Cochliobolus
244	Foot rot, various hosts	Aphanomyces spp.	Saprolegniales	Aphanomyces
245	Foot rot, various hosts	Phytophthora spp.	Peronosporales	Phytophthora
246	Foot rot, various hosts	Rhizoctonia spp.	Stereales	Rhizoctonia
247	Formosan termite	Coptotermes formosanus	Isoptera:	Coptotermes
248	Four-leaved water clover	Marsilea spp.	Marsileaceae	Marsilea
249	Foxtail grasses	Setaria spp.	Gramineae	Setaria
250	Foxtail, giant	Setaria faberi	Gramineae	Setaria
251	Foxtail, green	Setaria viridis	Gramineae	Setaria
252	Foxtail, yellow	Setaria glauca (= S. lutescens)	Gramineae	Setaria
253	Fresh water snails	Lymnaea spp.	Mollusca: Gastropoda	Lymnaea
254	Fringe rushes	Fimbristylis spp.	Cyperaceae	Fimbristylis
255	Frit fly	Oscinella frit	Diptera: Chloropidae	Oscinella
256	Frog eye, soya	Cercosporidium spp. (includes	Hyphales	Cercosporidium
257	Fruit flies	Dacus spp.	Diptera: Tephritidae	Dacus
258	Fruit flies	Drosophila spp.	Diptera: Drosophilidae	Drosophila
259	Fruit rot, strawberries	Mucor spp.	Mucorales	Mucor
260	Fruit rot, various hosts	Botrytis cinerea	Hyphales	Botrytis
261	Fruit tree red spider mite	Panonychus ulmi	Acari: Tetranychidae	Panonychus
262	Fruit tree red spider mite predator	Amblyseius finlandicus	Acari: Phytoseiidae	Amblyseius
263	Fruit tree red spider mite predator	Typhlodromus pyri	Acari: Phytoseiidae	Typhlodromus
264	Fuchsia	Fuchsia hybrida	Onagraceae	Fuchsia
265	Fungal virus vector	Polymyxa betae	Plasmodiophorales	Polymyxa
266	Fungi which produce no spores	Agonomycetales	Deuteromycotina	Agonomycetales
267	Fungi with no known sexual stage, or	Deuteromycetes	Deuteromycotina (=	Deuteromycetes
268	Fungi, sexually produced spores in	Ascomycotina		Ascomycotina
269	Fungus gnats, sciarid flies	Sciaridae	Diptera	Sciaridae
270	Furniture beetle	Anobium punctatum	Coleoptera: Anobiidae	Anobium
271	Fusarium foot and root rots, various	Fusarium culmorum	Hyphales	Fusarium
272	Fusarium wilt, various hosts	Fusarium oxysporum	Hyphales	Fusarium
273	Gall midges	Cecidomyiidae	Diptera	Cecidomyiidae
274	Gangrene, potatoes	Phoma exigua var. foveata	Deuteromycotina	Phoma
275	Garden wireworms	Athous spp.	Coleoptera: Elateridae	Athous
276	German cockroach	Blattella germanica	Dictyoptera: Blattidae	Blattella
277	Giant knotweed	Reynoutria sachalinensis	Polygonaceae	Reynoutria
278	Glasshouse potato aphid	Aulacorthum solani	Homoptera: Aphididae	Aulacorthum
279	Glasshouse whitefly	Trialeuroides vaporariorum	Homoptera.	Trialeuroides
280	Glasshouse whitefly parasitoid	Encarsia formosa	Hymenoptera:	Encarsia

281	Gloeosporium rot, apples	Glomerella cingulata	Polystigmatales	Glomerella
282	Gloeosporium rot, apples	Gloeosporium spp.	Deuteromycotina	Gloeosporium
283	Glume blotch, wheat	Leptosphaeria nodorum(=	Dothidiales	Leptosphaeria
284	Glume spots, various hosts	Septoria spp.	Sphaeropsidales	Septoria
285	Golden hamster	Mesocricetus auratus	Rodentia: Cricetidae	Mesocricetus
286	Gooseberry bryobia mite	Bryobia ribis	Acari: Tetranychidae	Bryobia
287	Goosegrass	Eleusine indica	Gramineae	Eleusine
288	Gooseweed	Sphenoclea zeylanica	Sphenocleaceae	Sphenoclea
289	Grain beetles	Cryptolestes spp.	Coleoptera: Cucujidae	Cryptolestes
290	Grain mites	Acarus spp.	Acari: Acaridae	Acarus
291	Grass and cereal flies	Opomyza spp.	Diptera: Opomyzidae	Opomyza
292	Grass moth	Chrysoteuchia caliginosellus (=	Lepidoptera: Pyralidae	Chrysoteuchia
293	Grasshoppers	Acrididae	Saltatoria	Acrididae
294	Greasy blotch, carnation	Zygopiala jamaicensis	Spaeropsidales	Zygopiala
295	Green leafhopper	Empoasca fabae	Homoptera: Cicadellidae	Empoasca
296	Green leafhoppers	Nephotettix spp.	Homoptera: Cicadellidae	Nephotettix
297	Green mould, citrus	Penicillium digitatum	Hyphales	Penicillium
298	Green rice leafhopper	Nephotettix impicticepts	Homoptera: Cicadellidae	Nephotettix
299	Green rice leafhopper	Nephotettix cincticeps	Homoptera: Cicadellidae	Nephotettix
300	Gypsy moth	Lymantria dispar	Lepidoptera:	Lymantria
301	Halo blight, beans	Pseudomonas phaseolicola	Eubacteriales	Pseudomonas
302	Harvester ants	Pogonomyrmex spp.	Hymenoptera:	Pogonomyrmex
303	Head louse	Pediculus capitis	Phthiraptera: Pediculidae	Pediculus
304	Head smut, maize	Sphacelotheca reiliana	Ustilaginales	Sphacelotheca
305	Helmet scale	Saissetia coffeae	Homoptera: Coccidae	Saissetia
306	Helminthosporium blight, rice	Helminthosporium oryzae	Hyphales	Helminthosporium
307	Hemispherical scale	Saissetia coffeae	Homoptera: Coccidae	Saissetia
308	Hemp sesbania	Sesbania exaltata	Leguminosae	Sesbania
309	Horn fly	Haematobia irritans	Diptera: Muscidae	Haematobia
310	Hornweed, common	Ceratophyllum demersum	Ceratophyllaceae	Ceratophyllum
311	Horse flies	Tabanus spp.	Diptera: Tabanidae	Tabanus
312	House fly	Musca domestica	Diptera: Muscidae	Musca
313	House longhorn beetle	Hylotrupes bajulus	Coleoptera:	Hylotrupes
314	House mosquito	Culex fatigans (= C.	Diptera	Culex
315	House mouse	Mus domesticus, Mus musculus	Rotentia: Muridae	Mus
316	Human body louse	Pediculus humanus	Phthiraptera: Pediculidae	Pediculus
317	Itch mite	Sarcoptes scabiei	Acari: Sarcoptidae	Sarcoptes
318	Ivy	Hedera helix	Araliaceae	Hedera
319	Ixodid ticks	Ixodidae	Acari	Ixodidae
320	Japanese bulrush	Scirpus juncoides	Cyperaceae	Scirpus
321	Japanese field vole	Microtus montebelli	Rotentia: Muridae	Microtus
322	Japanese knotweed	Reynoutria japonica (=	Polygonaceae	Reynoutria
323	Jimson weed	Datura stramonium	Solanaceae	Datura
324	Johnson grass	Sorghum halepense	Gramineae	Sorghum
325	Joint vetches	Aeschynomene spp.	Leguminosae	Aeschynomene
326	Khapra beetle	Trogoderma granarium	Coleoptera: Dermestidae	Trogoderma
327	Knapweeds	Centaurea spp.	Compositae	Centaurea

328	Knot grass	Polygonum aviculare	Polygonaceae	Polygonum
329	Knotweeds	Polygonum spp.	Polygonaceae	Polygonum
330	Kyllinga, green	Cyperus brevifolius	Cyperaceae	Cyperus
331	Lace bugs	Tingidae	Heteroptera	Tingidae
332	Large fruit flies	Tephritidae	Diptera	Tephritidae
333	Large white butterfly	Pieris brassicae	Lepidoptera: Pieridae	Pieris
334	Late flowering cyperus	Cyperus serotinus	Cyperaceae	Cyperus
335	Leaf and pod spot, peas	Ascochyta pinodes, Ascochyta	Sphaeropsidales	Ascochyta
337	Leaf blast, rice	Pyricularia oryzae	Hyphales	Pyricularia
338	Leaf blight, rice	Xanthomonas oryzae	Eubacteriales	Xanthomonas
339	Leaf blotch, barley and rye	Rhynchosporium secalis	Hyphales	Rhynchosporium
340	Leaf blotches, etc., various hosts	Marssonina spp.	Melanconiales	Marssonina
341	Leaf miners	Agromyza spp., Liriomyza spp.,	Diptera: Agromyzidae	Agromyza
344	Leaf mould, tomato	Fulvia fulva	Hyphales	Fulvia
345	Leaf scorch, apples	Gymnosporangium spp.	Uredinales	Gymnosporangium
346	Leaf scorch, strawberry	Diplocarpon earliana	Helotiales	Diplocarpon
347	Leaf smuts, various hosts	Urocystis spp.	Ustilaginales	Urocystis
348	Leaf spot, apple	Botryosphaeria obtusa (=	Dothidiales	Botryosphaeria
350	Leaf spot, beans	Ascochyta fabae	Sphaeropsidales	Ascochyta
351	Leaf spot, beet crops	Cercospora beticola, Ramularia	Hyphales	Cercospora
352	Leaf spot, currants, gooseberry	Pseudopeziza ribis	Helotiales	Pseudopeziza
353	Leaf spot, melon	Corynespora melonis	Hyphales	Corynespora
354	Leaf spot, soya	Cercosporidium spp. (includes	Hyphales	Cercosporidium
355	Leaf spot, sunflowers	Diaporthe helianthi	Diaporthales	Diaporthe
356	Leaf spots, grasses	Rhynchosporium spp.	Hyphales	Rhynchosporium
336	Leaf spots, various hosts	Septoria spp.	Sphaeropsidales	Septoria
349	Leaf spots, various hosts	Mycosphaerella spp.	Dothidiales	Mycosphaerella
357	Leaf spots, various hosts	Alternaria spp., Cercospora	Hyphales	Alternaria
358	Leaf spots, various hosts	Ascochyta spp., Septoria spp.	Sphaeropsidales	Ascochyta
359	Leaf stripe, barley	Pyrenophora graminea	Dothidiales	Pyrenophora
342	Leaf-mining moths	Leucoptera spp.	Lepidoptera: Lyonetiidae	Leucoptera
343	Leaf-mining moths	Phyllonorycter spp.	Lepidoptera:	Phyllonorycter
360	Leafhoppers	Cicadellidae	Homoptera	Cicadellidae
361	Leatherjackets	Tipula spp.	Diptera: Tipulidae	Tipula
362	Lemon-shaped cyst nematodes	Heterodera spp.	Nematoda:	Heterodera
363	Lesser armyworm	Spodoptera exigua	Lepidoptera: Noctuidae	Spodoptera
364	Lesser bandicoot mole rat	Bandicota benghalensis	Rotentia: Muridae	Bandicota
365	Lesser grain borer	Rhyzopertha dominica	Coleoptora: Bostrichidae	Rhyzopertha
366	Lesser house fly	Fannia canicularis	Diptera: Muscidae	Fannia
367	Light leaf spot, brassicas	Pyrenopeziza brassicae	Helotiales	Pyrenopeziza
368	Liverworts	Bryophyta	Bryophyta	Bryophyta
369	Locusts	Acrididae	Saltatoria	Acrididae
370	Long-nosed cattle louse	Linognathus vituli	Phthiraptera:	Linognathus
371	Long-tailed field mouse	Apodemus sylvaticus	Rotentia: Muridae	Apodemus
372	Loose silky-bent	Apera spica-venti	Gramineae	Apera
373	Loose smut, barley, wheat	Ustilago nuda	Ustilaginales	Ustilago
374	Maize stalk borer	Diatraea saccharalis	Lepidoptera: Pyralidae	Diatraea

375	Maize stalk rot	Gibberella fujikuroi	Hypocreales	Gibberella
376	Maize weevil	Sitophilus zeamais	Coleoptera:	Sitophilus
377	Mange mites	Chorioptes spp., Notocdres spp.,	Acari: Psoroptidae	Chorioptes
378	Mangold flea beetle	Chaetocnema concinna	Coleoptera:	Chaetocnema
379	Mangold fly	Pegomya hyoscamni	Diptera: Anthomyiidae	Pegomya
380	Mayweed, scentless	Tripleurospermum maritimum		Tripleurospermum
381	Mayweeds	Chamomilla spp., Matricaria	Compositae	Chamomilla
382	McDaniel's spider mite	Tetranychus mcdanieli	Acari: Tetranychidae	Tetranychus
383	Meadow grass, annual	Poa annua	Gramineae	Poa
384	Meadow-grass, rough	Poa trivialis	Gramineae	Poa
385	Mealworms	Alphitobius spp., Tenebrio spp.	Coleoptera:	Alphitobius
386	Mealybugs	Pseudococcus spp.	Homoptera:	Pseudococcus
387	Mediterranean black scale	Saissetia oleae	Homoptera: Coccidae	Saissetia
388	Mediterranean fruit fly	Ceratitis capitata	Diptera	Ceratitis
389	Melanosis, citrus	Diaporthe citri	Diaporthales	Diaporthe
390	Melon and cotton aphid	Aphis gossypii	Homoptera: Aphididae	Aphis
391	Mexican bean beetle	Epilachna varivestis	Coleoptera:	Epilachna
392	Mice	Mus spp.	Rotentia: Muridae	Mus
393	Millepedes	Diplopoda	Myriapoda	Diplopoda
394	Millet, Texas	Panicum texanum	Gramineae	Panicum
395	Minute black ladybird	Stethorus punctum	Coleoptera:	Stethorus
396	Mites	Aculops spp., Calepitrimerus	Acari: Eriophyidae	Aculops
397	Mock cypress	Kochia scoparia	Chenopodiaceae	Kochia
398	Mole crickets	Gryllotalpa spp.	Saltatoria	Gryllotalpa
399	Moles	Talpa spp.	Insectivora: Talpidae	Talpa
400	Monilinia leaf blight, apple	Monilinia mali	Helotiales	Monilinia
401	Morning glory, ivyleaf	Ipomoea hederacea	Convolvulaceae	Ipomoea
402	Morning glory, tall	Ipomoea purpurea	Convolvulaceae	Ipomoea
403	Mosquitoes	Culex spp.	Diptera	Culex
404	Moss	Polytrichum juniperinum	Musci	Polytrichum
405	Moss, aquatic	Najas guadalupensis	Najadaceae	Najas
406	Mosses	Bryophyta	Bryophyta	Bryophyta
407	Moth flies	Psychodidae	Diptera	Psychodidae
408	Mugwort; wormwood	Artemisia vulgaris	Compositae	Artemisia
409	Muscid flies	Musca spp.	Diptera: Muscidae	Musca
410	Mushroom cecid	Heteropeza pygmaea	Diptera: Cecidomyiidae	Heteropeza
411	Mushroom sciarid	Lycoriella auripila	Diptera: Sciaridae	Lycoriella
412	Mushrooms, etc.	Agaricales		Agaricales
413	Neck rot, onions	Botrytis allii	Hyphales	Botrytis
414	Needle nematodes	Longidorus spp.	Nematoda	Longidorus
415	Nematodes	Nematoda		Nematoda
416	Net blotch, barley	Pyrenophora teres	Dothidiales	Pyrenophora
417	Nettle, common	Urtica dioica	Urticaceae	Urtica
418	Nettle, small	Urtica urens	Urticaceae	Urtica
419	Nettles	Urtica spp.	Urticaceae	Urtica
420	Nipplewort	Lapsana communis	Compositae	Lapsana
421	Noctuid moths	Noctuidae	Lepidoptera	Noctuidae

422	Northern leaf blight, maize	Helminthosporium turcicum	Hyphales	Helminthosporium
423	Nutgrass	Cyperus rotundus	Cyperaceae	Cyperus
424	Nutsedges	Cyperus spp.	Cyperaceae	Cyperus
425	Oat, sterile	Avena sterilis	Gramineae	Avena
426	Oats (wild and cultivated)	Avena spp.	Gramineae	Avena
427	Old World bollworm	Helicoverpa armigera	Lepidoptera: Noctuidae	Helicoverpa
428	Olive fruit fly	Dacus oleae	Diptera: Tephritidae	Dacus
429	Onion couch	Arrhenatherum elatius var.	Gramineae	Arrhenatherum
430	Onion thrips	Thrips tabaci	Thysanoptera: Thripidae	Thrips
431	Oriental tobacco budworm	Helicoverpa assulta	Lepidoptera: Noctuidae	Helicoverpa
432	Ox warble fly	Hypoderma bovis	Diptera: Oestridae	Hypoderma
433	Pacific rat	Rattus hawaiiensis	Rotentia: Muridae	Rattus
434	Pale persicaria	Polygonum lapathifolium	Polygonaceae	Polygonum
435	Palm rat	Rattus tiomanicus	Rotentia: Muridae	Rattus
436	Panic grasses	Panicum spp.	Gramineae	Panicum
437	Paralysis tick	Ixodes holocyclus	Acari: Ixodidae	Ixodes
438	Parasitic yeasts	Candida spp.	Endomycetales	Candida
439	Pea cyst nematode	Heterodera goettingiana	Nematoda:	Heterodera
440	Pea weevils	Sitona spp.	Coleoptera:	Sitona
441	Peach leaf-curl	Taphrina deformans	Taphrinales	Taphrina
442	Peach-potato aphid	Myzus persicae	Homoptera	Myzus
443	Pear leaf blister moth	Leucoptera malifoliella	Lepidoptera: Lyonetiidae	Leucoptera
444	Pear rust	Gymnosporangium fuscum	Uredinales	Gymnosporangium
445	Pear rust mite	Epitrimerus pyri	Acari: Eriophyidae	Epitrimerus
446	Pearly green lacewing	Chrysoperla carnea	Neuroptera: Chrysopidae	Chrysoperla
447	Penicillium rots	Penicillium spp.	Hyphales	Penicillium
448	Persicaria	Polygonum persicaria	Polygonaceae	Polygonum
449	Petunia	Petunia spp.	Solanaceae	Petunia
450	Pharaoh's ant	Monomorium pharaonis	Hymenoptera:	Monomorium
451	Pheidole ants	Pheidole megacephala	Hymenoptera:	Pheidole
452	Pickerel weed	Monochoria vaginalis	Pontederiaceae	Monochoria
453	Pimpernel, false	Lindernia procumbens	Scrophulariaceae	Lindernia
454	Pine processionary caterpillar	Thaumetopoea pityocampa	Lepidoptera:	Thaumetopoea
455	Pink bollworm	Pectinophora gossypiella	Lepidoptera: Gelechiidae	Pectinophora
456	Plantains	Plantago spp.	Plantaginaceae	Plantago
457	Planthoppers	Nilaparvata spp.	Homoptera: Delphacidae	Nilaparvata
458	Plum rust	Tranzchelia pruni-spinosi	Uredinales	Tranzchelia
459	Pod rot, cocoa	Monilia roreri	Hyphales	Monilia
460	Pollen beetle	Meligethes aeneus	Coleoptera: Nitidulidae	Meligethes
461	Pondweed, American	Potamogeton distinctus	Potamogetonaceae	Potamogeton
462	Pondweeds	Potamogeton spp.	Potamogetonaceae	Potamogeton
463	Poppies	Papaver spp.	Papaveraceae	Papaver
464	Post-harvest rot	Fusarium coeruleum	Hyphales	Fusarium
465	Post-harvest rots	Rhizopus spp.	Mucorales	Rhizopus
466	Post-harvest rots	Sclerotium spp.	Agonomycetales	Sclerotium
467	Potato aphid	Macrosiphum euphorbiae	Homoptera: Aphididae	Macrosiphum
468	Potato cyst nematodes	Globodera spp.	Nematoda:	Globodera

469	Potato leafhopper	Eupterycyba jucunda	Homoptera: Cicadellidae	Eupterycyba
470	Potato moth	Phthorimaea operculella	Lepidoptera: Gelechiidae	Phthorimaea
471	Powdery mildew	Oidium hevea	Erysiphales	Oidium
472	Powdery mildew	Leveillula spp.	Erysiphales	Leveillula
473	Powdery mildew, apple	Podosphaera leucotricha	Erysiphales	Podosphaera
474	Powdery mildew, beet crops	Erysiphe betae	Erysiphales	Erysiphe
475	Powdery mildew, cereals, grasses	Erysiphe graminis	Erysiphales	Erysiphe
476	Powdery mildew, cucurbits	Erysiphe cichoracearum	Erysiphales	Erysiphe
477	Powdery mildew, cucurbits	Sphaerotheca fuliginea	Erysiphales	Sphaerotheca
478	Powdery mildew, grapevines	Uncinula necator	Erysiphales	Uncinula
479	Powdery mildew, rose	Sphaerotheca pannosa	Erysiphales	Sphaerotheca
480	Powdery mildew, various hosts	Phyllactinia spp.	Erysiphales	Phyllactinia
481	Prairie dogs	Cynomys spp.	Rodentia: Sciuridae	Cynomys
482	Predacious midges	Cecidomyiidae	Diptera	Cecidomyiidae
483	Prickly pear cacti	Opuntia spp.	Cactaceae	Opuntia
484	Primitive fungi (Phycomycetes)	Mastigomycotina		Mastigomycotina
486	Psyllids	Psylla spp.	Homoptera: Psyllidae	Psylla
487	Purslane	Portulaca oleracea	Portulacaceae	Portulaca
488	Pygmy beetle	Atomaria linearis	Coleoptera:	Atomaria
489	Pyralid moths	Pyralidae	Lepidoptera	Pyralidae
490	Quackgrass	Elymus repens	Gramineae	Elymus
491	Rabbit	Oryctolagus cuniculus	Leporidae: Lagomorpha	Oryctolagus
492	Rabbit fur mite	Cheyletiella parasitivorax	Acari: Cheyletidae	Cheyletiella
493	Ragweed, common	Ambrosia artemisifolia	Compositae	Ambrosia
494	Rape	Brassica napus	Cruciferae	Brassica
495	Ray blight, chrysanthemum	Didymella ligulicola	Dothidiales	Didymella
497	Red core, strawberry	Phytophthora fragariae	Peronosporales	Phytophthora
498	Red crevice tea mite	Brevipalpus phoenicis	Acari: Tenuipalpidae	Brevipalpus
499	Red dead-nettle	Lamium purpureum	Labiatae	Lamium
500	Red spider mites	Panonychus spp.	Acari: Tetranychidae	Panonychus
501	Red thread, turf	Laetisaria fuciformis	Aphyllophorales	Laetisaria
496	Red-billed quelea	Quelea quelea	Passeriformes: Ploceidae	Quelea
502	Redroot pigweed	Amaranthus retroflexus	Amaranthaceae	Amaranthus
503	Redshank	Polygonum persicaria	Polygonaceae	Polygonum
504	Rhizomania virus	Polymyxa betae	Plasmodiophorales	Polymyxa
505	Rhododendron	Rhododendron ponticum	Ericaceae	Rhododendron
506	Rice brown planthopper	Nilaparvata lugens	Homoptera: Delphacidae	Nilaparvata
507	Rice leaf beetle	Oulema oryzae	Coleoptera:	Oulema
508	Rice leaf roller	Cnaphalocrocis medinalis	Lepidoptera: Pyralidae	Cnaphalocrocis
509	Rice leaf scald	Monographella nivalis	Sphaeriales	Monographella
510	Rice sheath blight	Pellicularia sasakii	Tulasnellales	Pellicularia
511	Rice stalk borer	Chilo suppressalis	Lepidoptera: Pyralidae	Chilo
512	Rice stem borer	Chilo plejadellus	Lepidoptera: Pyralidae	Chilo
513	Rice water weevil	Lissorhoptrus oryzophilus	Coleoptera:	Lissorhoptrus
514	Rice weevil	Sitophilus oryzae	Coleoptera:	Sitophilus
515	Ring-spot, brassicas	Mycosphaerella brassicicola	Dothidiales	Mycosphaerella
516	Root flies	Anthomyiidae, Delia spp. (=	Diptera: Anthomyiidae	Anthomyiidae,

519	Root rot, brassicas	Phytophthora megasperma	Peronosporales	Phytophthora
520	Root rot, cereals, grasses	Cochliobolus sativus	Dothidiales	Cochliobolus
521	Root rot, tomato	Colletotrichum coccodes	Melanconiales	Colletotrichum
522	Root rots, various hosts	Aphanomyces spp.	Saprolegniales	Aphanomyces
523	Root rots, various hosts	Phoma spp.	Deuteromycotina	Phoma
524	Root rots, various hosts	Pythium spp.	Peronosporales	Pythium
525	Root rots, various hosts	Rhizoctonia spp.	Stereales	Rhizoctonia
517	Root-knot nematodes	Meloidogyne spp.	Nematoda	Meloidogyne
518	Root-lesion nematodes	Pratylenchus spp.	Nematoda:	Pratylenchus
526	Rose aphid	Macrosiphum rosae	Homoptera: Aphididae	Macrosiphum
527	Rose thrips	Thrips fuscipennis	Thysanoptera: Thripidae	Thrips
528	Rot, various crops	Phytophthora palmivora	Peronosporales	Phytophthora
529	Rots of stems, storage organs, etc.,	Sclerotinia sclerotiorum	Helotiales	Sclerotinia
531	Rots, various hosts	Pellicularia spp.	Tulasnellales	Pellicularia
532	Rots, various hosts	Sclerotium rolfsii	Agonomycetales	Sclerotium
530	Rots, various hosts (Imperfect fungi	Fusarium spp.	Hyphales	Fusarium
533	Rough Cocklebur	Xanthium strumarium	Compositae	Xanthium
534	Roughseed bulrush	Scirpus mucronatus	Cyperaceae	Scirpus
535	Rubbery rot, potatoes	Geotrichum candidum	Hyphales	Geotrichum
536	Runch	Raphanus raphanistrum	Cruciferae	Raphanus
537	Rush, flowering	Butomus umbellatus	Butomaceae	Butomus
538	Russian thistle	Salsola kali	Chenopodiaceae	Salsola
540	Rust fungi	Uredinales	Basidiomycotina	Uredinales
541	Rust mite, apple	Aculus schlechtendali	Acari: Eriophyidae	Aculus
542	Rust mites	Aculus spp.	Acari: Eriophyidae	Aculus
543	Rust mites	Phyllocoptruta spp.	Acari: Eriophyidae	Phyllocoptruta
539	Rust, beet crops	Uromyces betae	Uredinales	Uromyces
545	Rust, roses	Phragmidium mucronatum	Uredinales	Phragmidium
546	Rust, soya	Phakopsora pachyrhizi	Uredinales	Phakopsora
547	Rust, various hosts	Puccinia spp., Uromyces spp.	Uredinales	Puccinia
544	Rust-red flour beetle	Tribolium castaneum	Coleoptera:	Tribolium
548	Ryegrass, italian	Lolium multiflorum	Gramineae	Lolium
549	Ryegrass, perennial	Lolium perenne	Gramineae	Lolium
550	Ryegrasses	Lolium spp.	Gramineae	Lolium
551	San José scale	Comstockaspis perniciosus	Homoptera: Coccidae	Comstockaspis
552	Saprophytic fungi	Paecilomyces spp.	Hyphales	Paecilomyces
553	Saramatta grass	Ischaemum rugosum	Gramineae	Ischaemum
554	Saw-toothed grain beetle	Oryzaephilus surinamensis	Coleoptera: Cucujidae	Oryzaephilus
555	Sawflies	Diprion spp.	Hymenoptera:	Diprion
556	Scab, apples	Venturia inaequalis	Dothidiales	Venturia
557	Scab, cereals	Gibberella spp. (= various	Hypocreales	Gibberella
558	Scab, citrus	Elsinoe fawcettii	Dothidiales	Elsinoe
559	Scab, pears	Venturia pirina	Dothidiales	Venturia
560	Scabies mites, etc.	Sarcoptes spp.	Acari: Sarcoptidae	Sarcoptes
561	Scale insect	Didesmococcus brevipes	Homoptera: Coccidae	Didesmococcus
562	Scale insects	Coccus spp.	Homoptera: Coccidae	Coccus
563	Scale insects	Coccidae, Diaspidae,	Homoptera	Coccidae,

564	Scentless mayweed	Matricaria perforata (= M.	Compositae	Matricaria
565	Sclerotinia rots, various hosts	Sclerotinia spp.	Helotiales	Sclerotinia
566	Scuttle flies	Megaselia spp.	Diptera: Phoridae	Megaselia
567	Sea club-rush	Scirpus maritimus	Cyperaceae	Scirpus
568	Sea-rush	Juncus maritimus	Juncaceae	Juncus
569	Sedges	Carex spp.	Cyperaceae	Carex
570	Seed-eating ants	Monomorium spp.	Hymenoptera:	Monomorium
571	Septoria leaf spot, wheat	Mycosphaerella graminicola	Dothidiales	Mycosphaerella
572	Sharp eyespot, cereals	Ceratobasidium cereale	Tulasnellales	Ceratobasidium
573	Shattercane	Sorghum bicolor	Gramineae	Sorghum
574	Sheep biting louse	Bovicola ovis	Phthiraptera:	Bovicola
575	Sheep ked	Melophagus ovinus	Diptera: Hippoboscidae	Melophagus
576	Sheep maggot fly	Lucilia sericata	Diptera: Calliphoridae	Lucilia
577	Sheep sucking louse	Linognathus ovillus	Phthiraptera:	Linognathus
578	Sheep tick	Ixodes ricinus	Acari: Ixodidae	Ixodes
579	Shepherd's purse	Capsella bursa-pastoris	Cruciferae	Capsella
580	Short-nose cattle louse	Haematopinus eurysternus	Phthiraptera:	Haematopinus
581	Shothole, prunus	Stigmina carpophila	Hyphales	Stigmina
582	Siam weed	Eupatorium odoratum(=	Compositae	Eupatorium
583	Sickle pod	Cassia obtusifolia	Leguminosae (Fabaceae)	Cassia
584	Silver scurf, potatoes	Helminthosporium solani	Hyphales	Helminthosporium
585	Skin spot, potatoes	Polyscytalum pustulans	Hyphales	Polyscytalum
586	Slaters	Isopoda	Crustacea	Isopoda
587	Slugs	Gastropoda	Mollusca	Gastropoda
588	Small brown planthopper	Laodelphax striatella	Homoptera: Delphacidae	Laodelphax
589	Small white butterfly	Pieris rapae	Lepidoptera: Pieridae	Pieris
590	Smartweed	Polygonum persicaria	Polygonaceae	Polygonum
591	Smooth sowthistle	Sonchus oleraceus	Compositae	Sonchus
592	Smooth witchgrass	Panicum dichotomiflorum	Gramineae	Panicum
593	Smut diseases, various hosts	Ustilago spp.	Ustilaginales	Ustilago
594	Smut, various hosts	Tilletia spp.	Ustilaginales	Tilletia
595	Snails	Gastropoda	Mollusca	Gastropoda
596	Snow mould, grasses, cereals	Microdochium nivalis	Hyphales	Microdochium
597	Snow rot, cereals	Typhula incarnata	Aphyllophorales	Typhula
598	Social wasps	Vespula spp.	Hymenoptera: Vespidae	Vespula
599	Sooty blotch, apple pear and citrus	Gloeodes pomigena	Sphaeropsidales	Gloeodes
600	Sooty mould	Cladosporium spp.	Hyphales	Cladosporium
601	Sorghum grasses	Sorghum spp.	Gramineae	Sorghum
602	South American leaf miner	Liriomyza huidobrensis	Diptera: Agromyzidae	Liriomyza
603	Southern root-knot nematode	Meloidogyne incognita	Nematoda	Meloidogyne
604	Soya bean looper	Anticarsia gemmatalis	Lepidoptera: Noctuidae	Anticarsia
605	Speedwell, common field	Veronica persica	Scrophulariaceae	Veronica
606	Speedwell, ivy-leaved	Veronica hederifolia	Scrophulariaceae	Veronica
607	Speedwell, slender	Veronica filiformis	Scrophulariaceae	Veronica
608	Spider mites	Tetranychus spp.	Acari: Tetranychidae	Tetranychus
609	Spike rush	Eleocharis acicularis	Cyperaceae	Eleocharis
610	Spiny bollworms	Earias spp.	Lepidoptera: Noctuidae	Earias

611	Spiny sida	Sida spinosa	Malvaceae	Sida
612	Spiral nematodes	Helicotylenchus spp.	Nematoda: Tylenchidae	Helicotylenchus
613	Spotted spurge	Euphorbia maculata	Euphorbiaceae	Euphorbia
614	Sprangletop, bearded	Leptochloa fascicularis (=	Gramineae	Leptochloa
615	Sprangletop, red	Leptochloa chinensis	Gramineae	Leptochloa
616	Spur blight, cane fruit	Didymella applanata	Dothidiales	Didymella
617	Stable fly	Stomoxys calcitrans	Diptera: Muscidae	Stomoxys
618	Stalk rots, various hosts	Diplodia spp.	Sphaeropsidales	Diplodia
619	Stem borers	Chilo spp.	Lepidoptera: Pyralidae	Chilo
620	Stem canker, sunflowers	Diaporthe helianthi	Diaporthales	Diaporthe
621	Stem nematode	Ditylenchus dipsaci	Nematoda: Tylenchidae	Ditylenchus
622	Stem rots, various hosts	Phoma spp.	Deuteromycotina	Phoma
623	Stinking chamomile	Anthemis cotula	Compositae	Anthemis
624	Stinking mayweed	Anthemis cotula	Compositae	Anthemis
625	Storage fungi	Aspergillus spp.	Hyphales	Aspergillus
626	Stubby-root nematodes	Trichodorus spp.	Nematoda	Trichodorus
627	Sucking lice	Linognathus spp.	Phthiraptera:	Linognathus
628	Sugar beet root maggot	Tetanops myopaeformis	Diptera: Otitidae	Tetanops
629	Summer fruit tortrix moth	Adoxophyes orana	Lepidoptera: Tortricidae	Adoxophyes
630	Sunflower	Helianthus annuus	Compositae	Helianthus
631	Symphilids	Symphyla spp.	Myriapoda	Symphyla
632	Tan spot, wheat	Pyrenophora tritici-repentis	Dothidiales	Pyrenophora
633	Tarsonemid mites	Tarsonemus spp. (=	Acari: Tarsonemidae	Tarsonemus
634	Tea leaf roller	Caloptilia theivora	Lepidoptera:	Caloptilia
635	Termites	Coptotermes spp.	Isoptera:	Coptotermes
636	Tetranychid mites	Eotetranychus spp.,	Acari: Tetranychidae	Eotetranychus
637	Texas citrus mite	Eutetranychus banksi	Acari: Tetranychidae	Eutetranychus
638	Thistle, creeping	Cirsium arvense	Compositae	Cirsium
639	Thistles	Carduus spp.	Compositae	Carduus
640	Thorn apple	Datura stramonium	Solanaceae	Datura
641	Thrips	Thrips spp.	Thysanoptera: Thripidae	Thrips
642	Ticks	Amblyomma spp.	Acari: Ixodidae	Amblyomma
643	Ticks	Boophilus microplus	Acari: Ixodidae	Boophilus
644	Ticks	Ixodes spp.	Acari: Ixodidae	Ixodes
645	Ticks	Rhipicephalus spp.	Acari: Ixodidae	Rhipicephalus
646	Tobacco budworm	Heliothis virescens	Lepidoptera: Noctuidae	Heliothis
647	Tobacco flea beetle	Epitrix hirtipennis	Coleoptera:	Epitrix
648	Tobacco whitefly	Bemisia tabaci	Homoptera: Aleyrodidae	Bemisia
649	Tomato canker	Clavibacter michiganensis	Eubacteriales	Clavibacter
650	Tomato leaf miner	Liriomyza bryoniae	Diptera: Agromyzidae	Liriomyza
651	Tomato pinworm	Keiferia lycopersicella	Lepidoptera: Gelechiidae	Keiferia
652	Tortrix moths	Tortrix spp.	Lepidoptera: Tortricidae	Tortrix
653	Tropical green rice leafhopper	Nephotettix nigropictus	Homoptera: Cicadellidae	Nephotettix
654	True crickets	Gryllidae	Saltatoria	Gryllidae
655	Tsetse flies	Glossina spp.	Diptera: Glossinidae	Glossina
656	Turnip gall weevil	Ceutorhynchus pleurostigmata	Coleoptera:	Ceutorhynchus
657	Turnip moth	Agrotis segetum	Lepidoptera: Noctuidae	Agrotis

658	Two-spotted spider mite	Tetranychus urticae	Acari: Tetranychidae	Tetranychus
659	Two-spotted spider mite predator	Phytoseiulus persimilis	Acari: Phytoseiidae	Phytoseiulus
660	Umbrella plant	Cyperus difformis	Cyperaceae	Cyperus
661	Valsa canker of apple	Valsa ceratosperma	Diaporthales	Valsa
662	Velvetleaf	Abutilon theophrasti	Malvaceae	Abutilon
663	Verticillium wilt, various hosts	Verticillium spp.	Hyphales	Verticillium
664	Vine weevil	Otiorhynchus sulcatus	Coleoptera:	Otiorhynchus
665	Wandering Jew	Commelina spp.	Commelinaceae	Commelina
666	Warble flies	Hypoderma spp.	Diptera: Oestridae	Hypoderma
667	Warehouse moth	Ephestia elutella	Lepidoptera: Pyralidae	Ephestia
668	Water duckweed	Pistia stratiotes	Araceae	Pistia
669	Water hyacinth	Eichhornia crassipes	Pontederiaceae	Eichhornia
670	Water plantain	Alisma plantago-aquatica	Alismataceae	Alisma
671	Water plantain, narrow leaved	Alisma lanceolatum	Alismataceae	Alisma
672	Water primroses	Jussiaea spp.	Onagraceae	Jussiaea
673	Water purslane	Ludwigia peploides	Onagraceae	Ludwigia
674	Water weed	Elodea canadensis	Hydrocharitaceae	Elodea
675	Weevils	Curculionidae	Coleoptera	Curculionidae
676	Western flower thrips	Frankliniella occidentalis	Thysanoptera: Thripidae	Frankliniella
677	Wheat bulb fly	Delia coarctata	Diptera: Anthomyiidae	Delia
679	White blister	Albugo candida	Peronosporales	Albugo
680	White leaf spot, oilseed rape	Pseudocercosporella capsellae	Hyphales	Pseudocercosporella
681	White leaf spot, strawberry	Mycosphaerella fragariae	Dothidiales	Mycosphaerella
682	White mould, mushrooms	Mycogone perniciosa	Hyphales	Mycogone
683	White mustard	Sinapis alba	Cruciferae	Sinapis
684	White rot, onion	Sclerotium cepivorum	Agonomycetales	Sclerotium
685	White rot, timber	Ganoderma spp.	Ganodermataceae	Ganoderma
678	White-backed planthopper	Sogatella furcifera	Homoptera: Delphacidae	Sogatella
686	Whiteflies	Bemisia spp.	Homoptera: Aleyrodidae	Bemisia
687	Wild oat	Avena fatua	Gramineae	Avena
688	Wild oat, winter	Avena sterilis ssp. ludoviciana	Gramineae	Avena
689	Wild pansies	Viola spp.	Violaceae	Viola
690	Wild pig	Sus scrofa	Artiodactyla: Suidae	Sus
691	Wild radish	Raphanus raphanistrum	Cruciferae	Raphanus
692	Wilts, various hosts (Imperfect fungi	Fusarium spp.	Hyphales	Fusarium
693	Wimmera ryegrass	Lolium rigidum	Gramineae	Lolium
694	Wireworms	Agriotes spp.	Coleoptera: Elateridae	Agriotes
695	Woodlice	Isopoda	Crustacea	Isopoda
696	Woolly aphid	Eriosoma lanigerum	Homoptera:	Eriosoma
697	Yeasts	Endomycetales	Ascomycotina	Endomycetales
698	Yellow cereal fly	Opomyza florum	Diptera: Opomyzidae	Opomyza
699	Yellow fever mosquito	Aedes aegypti	Diptera: Culicidae	Aedes
700	Yellow nutsedge	Cyperus esculentus	Cyperaceae	Cyperus
701	Yellow rust, cereals	Puccinia striiformis	Uredinales	Puccinia
702	Yellow underwing moth	Noctua pronuba	Lepidoptera: Noctuidae	Noctua
703	Yew	Taxus baccata	Taxaceae	Taxus
485	zygospores.	Zygomycotina		Zygomycotina

Primer ID	Sequence info
1	T P L K K K L D E F G oligo:5'-ACCCCTCTGAAGAAGAAGCTGraygarttygg-3' degen=16 temp=60.0
2	A V A A I P E G oligo:5'-GCCGTGGCCGCCathccngargg-3' degen=24 temp=64.2
3	T V I C S D K T G oligo:5'-CACCGTGATCTGCTCCgayaaracngg-3' degen=16 temp=62.1
4	D M V L A D D N oligo:5'-CCGACATGGTGCTGgcngaygayaa-3' degen=16 temp=60.9
5	R Y M I S S N I G E oligo:5'-CCGGTACATGATCTCCTCCaayrtnggnga-3' degen=64 temp=62.2
6	D K T G T L T T N ctrttytgnccGTGGGACTGGTGGT oligo:5'-TGGTGGTCAGGGTGccngtyttrtc-3' degen=16 temp=60.0
7	A M T G D G V N cgntactgnccGCTGCCGCACTTG oligo:5'-GTTCACGCCGTCGccngtcatngc-3' degen=16 temp=61.0
8	Y M I S S N I G E V atrtactadwsGAGGTTGTAGCCGCTCC oligo:5'-CCTCGCCGATGTTGGAGswdatcatrta-3' degen=24 temp=61.4
9	P V Q L L W V N L V ggncangtyraCGACACCCACTTGGACC oligo:5'-CCAGGTTCACCCACAGCarytgnacngg-3' degen=64 temp=61.8

Preferred Primer combinations for PCR of plant SERCA cDNA:

1-6, 1-7, 1-8, 1-9, 2-7, 2-8, 2-9, 3-7, 3-8 ,3-9 ,4-9 ,5-9

Primer ID	Sequence info
10	V I C S D K T G T oligo:5'-CCGTGATCTGCTCCGACaaracnggnac-3' degen=32 temp=63.4
11	A M T G D G V N oligo:5'-CGCCATGACCGGCgayggngtnaa-3' degen=32 temp=65.5
12	F I R Y M I S S N I G aartadkcnatGTACTAGAGGAGGTTGTAGCC oligo:5'-CCGATGTTGGAGGAGATCATGtanckdatraa-3' degen=48 temp=63.3

Preferred Primer combinations to isolate SERCA cDNA from all origins :

2-6, 2-12, 2-9, 10-12, 10-9, 11-12, 11-9

Claims:

1. A method of identifying compounds having pesticidal activity, which method comprises:

providing microscopic nematode worms expressing a pest SERCA protein, said protein being derived from a pest species, other than the *C. elegans* SERCA protein; and

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the nematode worm in the presence or absence of test compounds;

wherein a reduction in SERCA activity in the presence of a compound is taken as an indication that the compound has pesticidal activity.

2. A method of identifying compounds capable of down-regulating the activity of a sarco/endoplasmic reticulum calcium ATPase, which method comprises:

providing microscopic nematode worms expressing a pest SERCA protein, said protein being derived from a pest species, other than the *C. elegans* SERCA protein;

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the microscopic nematode worm in the presence or absence of test compounds; and

thereby identifying compounds capable of down-regulating the activity of SERCA.

3. A method as claimed in claim 1 or claim 2 wherein the microscopic nematode worm is *C. elegans*.

4. A method as claimed in any one of claims 1 to 3 wherein the pest species is an invertebrate.

5. A method as claimed in claim 4 wherein the invertebrate is an arthropod.

6. A method as claimed in claim 5 wherein the arthropod is an insect.

7. A method as claimed in claim 4 wherein the invertebrate is a nematode other than *C. elegans*.

8. A method as claimed in any one of claims 1 to 3 wherein the pest species is a rodent.

9. A method as claimed in any one of claims 1 to 3 wherein the pest species is a plant.

10. A method as claimed in any one of claims 1 to 3 wherein the pest species is a fungus.

11. A method as claimed in any one of the preceding claims wherein the *C. elegans* is transgenic *C. elegans* containing a transgene comprising nucleic acid encoding the pest SERCA protein operably linked to a promoter.

12. A method as claimed in any one of claims 1 to 11 wherein the microscopic nematode exhibits no or substantially reduced activity of the endogenous nematode SERCA protein in one or more tissues or cell types.

13. A method as claimed in claim 12 wherein the nematode have a mutant genetic background.

14. A method as claimed in claim 13 wherein the nematode is a mutant which exhibits no or substantially reduced expression of the endogenous nematode SERCA protein in one or more cell types or tissues.

15. A method as claimed in claim 14 wherein the nematode is mutant *C. elegans* which carries a loss-of-function or knock-out mutation in the chromosomal *C. elegans* sca-1 gene.

16. A method as claimed in claim 15 wherein the *C. elegans* have ok190 genetic background.

17. A method as claimed in claim 12 wherein expression of the endogenous nematode SERCA protein is inhibited in one or more tissues or cell types using double-stranded RNA inhibition.

18. A method as claimed in claim 12 wherein the nematodes are treated with a SERCA inhibitor to reduce the activity of the endogenous SERCA protein and the pest SERCA protein is resistant to inhibition by the said SERCA inhibitor.

19. A method as claimed in claim 18 wherein the pest SERCA protein is modified so as to be resistant to inhibition by the said SERCA inhibitor.

20. A method as claimed in claim 19 wherein the SERCA inhibitor is thapsigargin and the pest SERCA protein carries a thapsigargin resistance mutation.

21. A method as claimed in claim 20 wherein the thapsigargin resistance mutation is a single amino acid substitution equivalent to a Phe259Val substitution in the *C. elegans* SERCA protein.

22. A method as claimed in claim 11 wherein the transgene comprises nucleic acid encoding the pest SERCA protein operably linked to a promoter which is capable of directing tissue or cell-type specific gene

expression in a tissue or cell type which exhibits no or background activity of the endogenous nematode SERCA protein.

23. A method as claimed in claim 22 wherein the nematode is *C. elegans* and the promoter is capable of directing specific gene expression in one or more *C. elegans* neurons.

24. A method as claimed in claim 23 wherein the promoter is the *unc-119* promoter.

25. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is pharynx pumping efficiency.

26. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is egg laying behaviour.

27. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is mating behaviour.

28. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is Ca^{2+} concentration in one or more tissues or cell types.

29. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is defecation behaviour.

30. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is growth rate.

31. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is movement behaviour.

32. A method as claimed in any one of claims 1 to 24 wherein the indicator of SERCA activity is life/death of the *C. elegans*.

33. A method of identifying compounds having the potential to kill pests using the nematode worm *C. elegans*, which method comprises:

providing microscopic nematodes which exhibit wild-type activity of the endogenous nematode SERCA protein; and

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the nematodes in the presence or absence of test compounds;

wherein a reduction in SERCA activity in the presence of a compound is taken as an indication that the compound has the potential to kill pests.

34. A method of identifying compounds capable of down-regulating the activity of a sarco/endoplasmic reticulum calcium ATPase, which method comprises:

providing microscopic nematodes which exhibit wild-type activity of the endogenous nematode SERCA protein;

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the nematodes in the presence or absence of test compounds; and

thereby identifying compounds capable of down-regulating the activity of SERCA.

35. A method as claimed in claim 33 or claim 34 wherein the microscopic nematodes are *C. elegans*.

36. A method as claimed in claim 33 or claim 34 wherein the microscopic nematode strain is a wild-type strain.

37. A method as claimed in claim 33 or claim 34 wherein the microscopic nematode strain is a mutant strain.

38. A method as claimed in claim 37 wherein the mutant strain is a constitutive pharynx pumping mutant.

39. A method as claimed in any one of claims 33 to 38 wherein the indicator of SERCA activity is pharynx pumping efficiency.

40. A method as claimed in any one of claims 33 to 38 wherein the indicator of SERCA activity is egg laying behaviour.

41. A method as claimed in any one of claims 33 to 38 wherein the indicator of SERCA activity is mating behaviour.

42. A method as claimed in any one of claims 33 to 38 wherein the indicator of SERCA activity is Ca^{2+} concentration in one or more tissues or cell types.

43. A method as claimed in any one of claims 33 to 38 wherein the indicator of SERCA activity is defecation behaviour.

44. A method as claimed in any one of claims 33 to 38 wherein the indicator of SERCA activity is growth rate.

45. A method as claimed in any one of claims 33

to 38 wherein the indicator of SERCA activity is movement behaviour.

46. A method as claimed in any one of claims 33 to 38 wherein the indicator of SERCA activity is life/death of the *C. elegans*.

47. A method of identifying compounds having pesticidal activity, which method comprises:

providing cultured cells expressing a SERCA protein; and

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the cells in the presence or absence of test compounds;

wherein a reduction in SERCA activity in the presence of a compound is taken as an indication that the compound has pesticidal activity.

48. A method of identifying compounds capable of down-regulating the activity of a sarco/endoplasmic reticulum calcium ATPase, which method comprises:

providing cultured cells expressing a SERCA protein;

detecting a phenotypic, biochemical or behavioural indicator of SERCA activity in the cells in the presence or absence of test compounds; and

thereby identifying compounds capable of down-regulating the activity of SERCA.

49. A method as claimed in claim 48 or claim 49 wherein the cultured cells are derived from a pest species.

50. A method as claimed in claim 48 or claim 49 wherein the pest species is an insect.

51. A method as claimed in claim 48 or claim 49

wherein the cultured cells are eukaryotic host cells containing an expression vector comprising nucleic acid encoding a SERCA protein.

52. A method as claimed in claim 51 wherein the host cells are a cell line capable of growing in monolayer or suspension culture.

53. A method as claimed in claim 52 wherein the host cells are COS1, BHK21, L929, PC12, CV1, SWISS3T3, HT144, IMR32, HEPG2, MDCK, MCF7, HEK293, Hela, A549, SW48 or G361.

54. A method as claimed in any one of claims 51 to 53 wherein the SERCA protein is a pest SERCA protein.

55. A method as claimed in any one of claims 47 to 54 wherein the indicator of SERCA activity is intracellular Ca^{2+} concentration.

56. A method as claimed in claim 55 wherein the indicator of SERCA activity is Ca^{2+} concentration in the endoplasmic reticulum.

57. A method as claimed in any one of claims 47 to 54 wherein the indicator of SERCA activity is cellular apoptosis.

58. A method of identifying compounds having pesticidal activity, which method comprises:

isolating microsomes from cultured cells expressing a SERCA protein; and

measuring Ca^{2+} levels in the microsomes in the presence or absence of test compounds;

wherein a reduction in SERCA activity in the presence of a compound is taken as an indication that

the compound has pesticidal activity.

59. A method of identifying compounds capable of down-regulating the activity of a sarco/endoplasmic reticulum calcium ATPase, which method comprises:

isolating microsomes from cultured cells expressing a SERCA protein;

measuring Ca^{2+} levels in the microsomes in the presence or absence of test compounds; and

thereby identifying compounds capable of down-regulating the activity of SERCA.

60. A method as claimed in claim 58 or claim 59 wherein the cultured cells are derived from a pest species.

61. A method as claimed in claim 58 or claim 59 wherein the cultured cells are eukaryotic host cells containing an expression vector comprising nucleic acid encoding a pest SERCA protein.

62. A compound identified as having pesticidal activity using a method according to any one of claims 1 to 61.

Figure 1

Homology of PLANT SERCA proteins, indicating consensus sequences and primer locations

```
O23087     -----------------MEEEKSFSAWSWSVEQCLKEYKTRLDKGLTSEDVQIRRQKYGFNELAKEKGKPLWHLVLEQFDDTLVKILLGAAFISFVLAFLGEEHGSGSGFEAFVEPFVIV
Q42883     -----------------MEE-KPFPAWSWSVDQCLKEYQVKLEKGLSTYEVDKRRERYGLNELEKEKGKPLWRLVLEQFDDTLVKILLGAAFISFVLAYVNQDETGESGFEAYVEPLVIL
AAF73985   ---------------------------------------MPAQAHNTSNLALISSDERGTRLLDQFEDTLVRVLVAAAAVSFLLALSSS--AGTLTLAAFVEPLVIF
BAA90510   MGEAGQDAPPPP---EKGVEVEVFPAWARGVEECEARLGVSASRGLSSREAAARLRAHGPNELAEHPGPTLLQLVAQQFDDTLVRILLAAAAVSFALALSSS--AGAVTLSAFVEPLVIF
O04987     MGKGSEDLVKKESLNSTPVNSDTFPAWAKDVAECEEHFVVSREKGLSSDEVLKRHQIYGLNELEKPEGTSIFKLILEQFNDTLVRILLAAAVISFVLAFFDGDEGGEMGITAFVEPLVIF
Q9SWS8     ---------------------MEDAYARSVSEVLDFFGVDPTKGLSDSQVVHHSRLYGRNVLPEEKRTPFWKLVLNSFDDLLVKILIVAAIVSFVLALANG----ETGLTAFLEPFVIL
consensus          '   ''''' '' '''    '    ''''' ''  ' ' '' ''L''''' ''' '''''F'D'LV 'L''AA  SF'LA'      '' '' A''EP'VI'

O23087     LILILNAVVGVWQESNAEKALEALKEMQCESAKVLRDGNVLPNLP-ARELVPGDIVELNVGDKVPADMRVSGLKTS-TLRVEQSSLTGEAMPVLKGANLVVMDDCELQGKENMVFAGTTV
Q42883     WILVLNAIVGVWQESNAEKALEALKEMQGESAKVLRDGYLVPDFP-AKELVPGDIVELRVGDKVPADMRVATLKSS-TLRVEQSSLTGESMPVTKSTDFLATDDCELQAKENMVFAGTTV
AAF73985   LILVVNAAVGVWQEANAERRVDALREIQSHHAAVLRDARCVPRAPLARDLVPGDVVQLRVGAKVPADMRVPASRAPPSSASSRASLTGETASVNKTSRALPLEDADIQAKDCMVFAGTTV
BAA90510   LILVVNAAVGVWQETNAEKALEALREIQSDHAAVLRDGDWLPSLP-ARDLVPGDIVQLRVGDKVPADMRVLRLVTS-TLRVEQGSLTGETASVNKTAHQVPHDDADIQAKECMVFAGTTV
O04987     LILIVNAIVGIWQETNAEKALEALKEIQSQQATVMRDGTKVSSLP-AKELVPGDIVELRVGDKVPADMRVVALISS-TLRVEQGSLTGESEAVSKTTKHVD-ENADIQGKKCMVFAGTTV
Q9SWS8     LILAANAAVGVITETNAEKALEELRAYQANIATVLRNG-CFSILP-ATELVPGDIVEVTVGCKIPADLRMIEMSSN-TFRVDQAILTGESCSVEKDVDCTLTTNAVYQDKKNILFSGTDV
consensus  'IL''NA'VG'''E'NAE'''''L ''Q'  A V'R''  '' 'P A''LVPGD'V'''VG'K'PAD'R'  ' '' ''''''  'LTGE' 'V K'   '   '''''Q'K' ''F'GT'V
                                        1                                                                     2
                                    --------->                                                           ---------->
O23087     VNGSCVCIVTSIGMDTEIGKIQRQIHEASLEESETPLKKKLDEFGSRLTTAICIVCVLVWMINYKNFVSWDVVDGYKPVNIKFSFEKCTYYFKIAVALAVAAIPEGLPAVITTCLALGTR
Q42883     VNGSCICIVVNTGMCTEIGKIQRQIHDASMEESDTPLKKKLDEFGNRLTFAIGVVCLVVWAINYKYFLSWEVVDDW-PSDFRFSFEKCAYYFKIAVALAVAAIPEGLPSVITTCLALGTR
AAF73985   VNGAALCIVARTGMDTEIGAIHAQIHQASQEDDDTPLKKKLNEFGEALTKIIGLICALVWLINCKYFLTFDLQGGWVPRNITFSFEKCTYYFEIAVALAVAAIPEGLPAVITTCLALGTR
BAA90510   VNGSAICLVVHTGMATEIGKIHAQIHEAAQEDDDTPLKKKLNEFGEALTKIIGLICALVWLINVKYFLTFELDG-WMPRNIRFSFEKCTYYFEIAVALAVAAIPEGLPAVITTCLALGTR
O04987     VNGNCICLVTDTGMNTEIGRVHSQIQEAAQHEEDTPLKKKLNEFGEVLTMIIGLICALVWLINVKYFLSWEYVD-GWPRNFKFSFEKCTYYFEIAVALAVAAIPEGLPAVITTCLALGTR
Q9SWS8     VAGRGRAVVIGVGSNTAMGSIHDSMLQT--DDEATPLKKKLDEFGSFLAKVIAGICVLVWVVNIGHFSDPSHGG--------F-FKGAIHYFKIAVALAVAAIPEGLPAVVTTCLALGTK
consensus  V'G'''''V  'G' T''G''' ''''''''  'TPLKKKL EFG' L'''I'''C''VW''N ''F'''' '   ' ''''  F'F'''''YF IAVALAVAAIPEGLP'V'TTCLALGT'
                     3
                 -------->
O23087     KMAQKNAIVRKLPSVETLGCTTVICSDKTGTLTTNQMSATEFFTLGGKTT--TTRVFSVSGTTYDPK----DGGIVDWGCNNMDANLQAVAEICSICNDAGVFY--EGKLFRATGLPTEA
Q42883     KMAQKNAIVRKLQSVETLGCTTVICSDKTGTLTTNQMSVSEFFTLGRKTT--ACRVFGVEGTTYDPK----DGGIMNWNCCKMDANLLLMAEICAICNDAGVFC--DGRLFKATGLPTEA
AAF73985   KMAAKNALVRKLPSVETLGCTTVICSDKTGTLTSNKMSVAKLVAVGDSSQ--EVRTFKVDGTTYDPR----DGKIHDWPAGSIDANLETIAKVAAVCNDANVAH--SSHQYVATGMPTEA
BAA90510   KMAAKNALVRKLPSVETLGCTTVICSDKTGTLTTNQMSVAKLVAIGDAEG--KVRSFKVDGTTYDPR----DGRIHDWPAGRMDANLQTIAKISAVCNDASVAH--SSHQYTATGMPTEA
O04987     KMAQKNALVRKLPSVETLGCTTVICSDKTGTLTTNQMAVSKLVAMGSRIG--TLRSFNVEGTSFDPR----DGKIEDWPMGRMDANLQMIAKIAAICNDANVEQ--SDQQFVSRGMPTEA
Q9SWS8     KMARLNAIVRSLPSVETLGCTTVICSDKTGTLTTNMMSVSKICVVQSAEHGPMINEFLLVETTYAPEGTVFDSNGMQLDLPAQSPCLHHLAMCSSLCNDSILQYNPDKDSYEKIGESTEV
consensus  KMA''NA VR'L'SVETLGCTTVICSDKTGTLT'N'M''''''' '          ' F ' 'T'''P'    D' ' ''' ' ''''L' 'A'' ''CND' '    '  '  ''G''TE'
                                   <--------
                                       6
O23087     ALKVLVEKMGIPEKKN---SENIEEVTNFSDNGSSVKLACCDWWNKRSKKVATLEFDRVRKSMSVIVSEPNGQNRLLVKGAAESILERSSFAQLA-DGSLVALDESSREVILKKHSEMTS
Q42883     ALKVLVEKMGVPDSKARCKIRDAQIVSSYLIDRNTVKLGCCDWWMKRSKRVATLEFDRVRKSMGVIVREPNGSNRLLVKGAFESLLERSTYVQLA-DGSTVPLDESCRQLLLLKQLEMSS
AAF73985   ALKVLVEKMGLPGGKN-----------GLSLDP-SEILGCCAWWNNVAKRIATLEFDRTRKSMGVVVKTSSGSNALLVKGAVETLLERSSHIQLK-DGSVVPLDEKAKRTILASLHEMST
BAA90510   ALKVLVEKMGIPEGMN-----------GLSLDP-SETLGCCQWWSNVAKRIATLEFDRTRKSMGVIVKSKSGRNALLVKGAVENLLERSSHIQLQ-DGSVVPLDEKSRKAILENLHEMSI
O04987     ALKVLVEKMGFPEGLN-----------EASSD--GDVLRCCRLWSELEQRIATLEFDRDRKSMGVMVDSSSGNKLLLVKGAVENVLERSTHIQLL-DGSKRELDQYSRDLILQSLRDMSL
Q9SWS8     ALRVLAEKVGLPGFDS-------MPSALNMLSKHERASYCNHYWENQFKKVYVLEFTRDRKMMSVLCSHKQ-MDVMFSKGAPESIIARCNKILCNGDGSVVPLTAAGRAELESRFYSFGD
consensus  AL'VL'EK'G P''''               '''  '  ''C' 'W '  '' ''LEF'R RK'M'V''   '' ' '''KGA'E'''R''''''  DGS'''L'' ''  '' ' '''.
```

Figure 1 contd.

```
O23087     KGLRCLGLAYKDELGEFSDYSS-EEHPSHKKLLDPSSYSNIETNLIFVGVVGLRDPPREEVGRAIEDCRDAGIRVMVITGDNKSTAEAICCEIRLFSENEDLSQSSFTGKEFMSLPASRR
Q42883     KGLRCLGLAYKDDLGELSGYYA-ATHPAHKKLLDPSCYSSIESDLVFVGVVGLRDPPREEVHRAVNDCRRAGIKIMVITGDNKSTAEAVCREIQLFSNGENLRGSSFTGKEFMAFSSQQQ
AAF73985   NALRCLGFAYKEALAEFRTYDG-ENHPRHNVFVDPANYAAIETDLIFAGLVGLRDPPREEVYDAIEDCRAAGIRVMVITGDNKETAEAICREIGVFSPDEDITFKSLQGKEFMALE-DKK
BAA90510   KALRCLGFAYKEDLAEFASYDG-ENHPAHKLLLDPVNYAAIETNLIFTGLAGLRDPPREEVFDAIEDCRAAGIRVMVITGDNKETAEAICREIGVFSHDEDITLKSLTGKEFMALE-DKK
O04987     SALRCLGFAYSDVPSDFATYDGSEDHPAHQQLLNPSNYSSIESNLIFVGFVGLRDPPRKEVRQAIADCRTAGIRVMVITGDNKSTAEAICREIGVFEADEDISSRSLTGIEFMDVQ-DQK
Q9SWS8     ETLRCLALAFKTVP-----H-G-----QQTISYDN------ENDLTFIGLVGMLDPPREEVRDAMLACMTAGIRVIVVTGDNKSTAESLCRKIGAFDNLVDFSGMSYTASEFERLPAVQQ
consensus  ''LRCL' A''' ' ''  ''' ' ''''' '''''''' 'E' L'F'G''G''DPPR'EV 'A'''C' AGI'''V'TGDNK'TAE''C''I''F' '''''  S''''EF'''  '''

                                                                                             4                5
                                                                                     -------->        -------->
O23087     SEILSKSGGKVFSRAEPRHKQEIVRMLKEM---GEIVAMTGDGVN-DAPALKLADIGIAMG-ITGTEVAKEASDMVLADDNFSTIVSAVAEGRSIYNNMKAFIRYMISSNVGEVISIFLT
Q42883     IEILSQDGGKVFSRAEPRHKQEIVRMLKEM---GEIVAMTGDGVN-DAPALKLADIGIAMG-ITGTEVAKEASDMVLADDNFSTIVSAVAEGRSIYNNMKAFIRYMISSNVGEVISIFLT
AAF73985   TARLPVKGGLLFSRAEPRQQTRTIRGGLAEGRIGQVVAMTGDGVNVSAPALKLVDIGVAMGVITGTEVAKEASDMVLADDNFSTIVSAVGEGRSIYNNMKAFIRYMISSNIGEVASIFLT
BAA90510   TLLR-RKGGLLFSRAEPRHKQEIVRLLKED---GEVVAMTGDGVN-DAPALKLADIGVAMG-ITGTEVAKEASDMVLADDNFSTIVAAVGEGRSIYNNMKAFIRYMISSNIGEVASIFLT
O04987     NHLR-QTGGLLFSRAEPKHKQEIVRLLKED---GEVVAMTGDGVN-DAPALKLADIGVAMG-ISGTEVAKEASDMVLADDNFSTIVAAVGEGRSIYNNMKAFIRYMISSNIGEVASIFLT
Q9SWS8     TLAL--RRMTLFSRVEPSHKRMLVEALQKQ---NEVVAMTGDGVN-DAPALKKADIGIAMG--SGTAVAKSASDMVLADDNFASIVAAVAEGRAIYNNTRQFIRYMISSNIGEVVCIFVA
consensus  '  '   ''''FSR'EP''''''' '''     '''VAMTGDGVN 'APALK''DIG AMG ''GT'VAK'ASDMVLADDNF''IV AV EGR'IYNN'''FIRYMISSN'GEV''IF''
                                            <-------                                                       <--------
                                               7                                                               8

O23087     AALGIPECMIPVQLLWVNLVTDGPPATALGFNPADIDIMKKPPRKSDDCLIDSWVLIRYLVIGSYVGVATVGIFVLWYTQASFLGISLISDGHTLVSFTQLQNWSECSSWGTNFTATPYT
Q42883     AVLGIPECLIPVQLLWVNLVTDGPPATALGFNPADVDIMQKPPRKNTDALINSWVFFRYMVIGSYVGIATVGIFIVWYTQASFLGINIVSDGHTLVELSQLRNWGECSTW-TNFTVSPFK
AAF73985   SALGIPEGLIPVQLLWVNLVTDGPPATSLGFNPPDKDIMKKPPRRSDDTLITPWILFRYLVIGLYVGMAT-GILLIWYTHGSFMGIDLTGDGHTLVTYSQLSNWGQCSSW-TTSRPRLSP
BAA90510   SALGIPEGLIPVQLLWVNLVTDGPPATALGFNPPDKDIMKKPPRKSDDSLITPWILFRYLVIGLYVGIATVGIFVIWYTHGSFMGIDLTGDGHTLVSYSQLSNWGQCSSW-TTSRPRLSP
O04987     AALGIPEGMIPVQLLWVNLVTDGPPATALGFNPPDKDIMKKPPRRSDDSLITAWILFRYMVIGLYVGVATVGIFVIWYTHGSFMGIDLTGDGHTLVSYSQLSNWGQCSTW-NNFTVTPFT
Q9SWS8     AVLGIPDTLAPVQLLWVNLVTDGLPATAIGFNKQDSDVMKAKPRKVGEAVVTGWLFFRYLVIGVYVGLATVAGFIWWFVYS---------DGGPKLTYSELMNFETCALR----------
consensus  ''LGIP''''PVQLLWVNLVTDG'PAT''GFN''D'D'M'''PR'''' ''' W'''RY'VIG'YVG AT'''''W''' '''''''  DG''''''''L ''''C''' '''''' '''
                <--------
                   9

O23087     VAGGLRTIAFENNPCDYFTLGKVKPMTLSLTVLVAIEMFNSLNALSEDNSLLTMPPWRNPWLLVAMTVSFALHCVILYVPFLANVFGIVPLSFREWF--VVILVSFPVILIDEALKFIG-
Q42883     AGN--RLITFS-DPCEYFTVGKVKAMTLSLSVLVAIEMFNSLNALSEDNSLIKMPPWRNPWLLVAMSLSFALHSVILYVPFLADIFGIVPLSLYEWL--LVILLSAPVILIDEVLKFVGR
AAF73985   PEP--ERSRSTTDPCDYFHAGKVKATTLSLSVLVAIEMFNSLNAS-PDSCLLAMPPWVNPWLLVAMSVSFGLHFLILYVPLLATVFGIVPLSLNEWLSLVLLMVALPVVLIDEALKLAGR
BAA90510   AGA--RTFTFDDNPCEYFHGGKVKATTLSLSVLVAIEMFNSLNALSEDTSLLRMPPWVNPWLLLAMSVSFGLHFLILYVPFLAQVFGIVPLSLNEWL--LVLLVALPVVLIDEVLKFVGR
O04987     AGS--QTFSFDSNPCDYFQQGKIKASTLSLSVLVAIEMFNSLNALSEDGSLVTMPPWVNPWLLLAMAVSFGLHFVILYVPFLAQVFGIVPLSLNEWL--LVLAVSLPVILIDEVLKFVGR
Q9SWS8     --------ETT-YPCSIFEDR--HPSTVAMTVLVVVEMFNALNNLSENQSLLVITPRSNLWLVGSIILTMLLHVLILYVHPLAVLCAVTPLSWAEWT--AVLYLSFPVIIIDELLKFLSR
consensus  ''    ''  '  'PC''F  ''''' T''''VLV''EMFN'LN''''' 'L' ''P''N'WL'''''''''LH' ILYV''LA '''''PLS''EW'  '''''''PV''IDE'LK''''

O23087     RCRRTRIKKKIKTM-----------------------------
Q42883     RRRRTKLKAA---------------------------------
AAF73985   CTSP-ASGPTRRSRKKKQKASSERRLTFDLRAQLLNHSINHVNKR
BAA90510   CTS--SSGPKRRTRK--QK--GE--------------------
O04987     CTSGYRYSPRTLSTK--QK--EE--------------------
Q9SWS8     NTG-MRFRFRLRKADLLPKDRRDK-------------------
consensus  '''  '  '  '  '  '  ''   '
```

Figure 2

Homology of known SERCA proteins indicating consensus sequences and primer location

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O96608       1 -----------------MALLSLPATPSTMDASAVTKCVRVDAKRGLPADEVEERRRQFGTNELPTKPSTPFWKLILAQFEDTLVRILLFAAMTSFVMALFEKNA------GDFVEPFII
ATC_TRYBB    1 -----------------MLPENLPTDPAAMTPAAVAAALRVDTKVGLSSNEVEERRQAFGINELPSEPPTPFWKLVLAQFEDTLVRILLLAATVSFAMAVVENNA------ADFVEPFII
O09489       1 ----MSKLGGHPSRPDHPAVLVLPDDPRSMDGHLICSLLEVKEAHGLAQDEVDRRLHEFGKNGFPTGSSTPFWKLVVGQFEDTLVRILLLAAFVSFCLAVLENNV------MDLVEPFII
O77070       1 -----------------------MEYAHTKSTEEVLEYFNVE-ESGLSEEQVKANTEKYGPNELPTEEGKPLWELILEQFDDLLVKILLLAAIISFVLVWFEESE---EQVTAFVEPFVI
O96039       1 -----------------------MEYAHTKSCEEVLEYFNVE-TDGLSEEQVKTNTEKYGPNELPTEEGKPLWELILEQFDDLLVKILLLAAIISFVLAWFEESE---EQVTAFVEPFVI
O96696       1 -----------------------MEDAHSKSVDEVLGYFGTDPDKGLSADQVKRNQDKYGPNELPAEEGKSIWQLVLEQFDDLLVKILLLAAIISFVLALFEEHE---DAFSAFVEPFVI
ATC1_DROME   1 -----------------------MEDGHSKTVEQSLNFFGTDPERGLTLDQIKANQKKYGPNELPTEEGKSIWQLVLEQFDDLLVKILLLAAIISFVLALFEEHE---ETFTAFVEPLVI
O17314       1 -----------------------MDDAHCFPVEDVVAKFGVNIENGLSASQVKDYQAKYGPNELPAEEGKSLLQLILEQFYDLLVKILLLAAIISFVLACFEEGE---ETVTAFVEPFVI
Q9XTG6       1 -----------------------MEDAHAKDANEVCKFFGTG-PEGLTPQQVETLRNKYGENEMPAEEGKSLWELILEQFDDLLVKILLLAAIISFVLALFEEHEDQTEAVTAFVEPFVI
O96527       1 -----------------------METAFSKTVDEVLHHFESDPENGLSDEQIKKQTAKFGPNELPAEESKAIWQLVLEQFDDLLVKILLMAAIISFVLALFEENE---ESISAFVEPLVI
O60900       1 -----------------------MEAAHLLPAADVLRHFSVTAEGGLSPAQVTGARERYGPNELPSEEGKSLWELVLEQFEDLLVRILLLAALVSFVLAWFEEGE---ETTTAFVEPLVI
Q64517       1 -----------------------MEEAHLLSAADVLRRFSVTAEGGLSLEQVTDARERYGPNELPTEEGKSLWELVVEQFEDLLVRILLLAALVSFVLAWFEEGE---ETTTAFVEPLVI
Q9YGL9       1 -----------------------MEAAHSVPVQDVLSRFGVAESCGLSPEQVRRNREKYGPNELPAEERKSLWELVLEQFEDLLVRILLMAAFLSFILAWFEEGE---ESTTAFVEPIVI
ATC2_MOUSE   1 -----------------------MENAHTKTVEEVLGHFGVNESTGLSLEQVKKLKERWGSNELPAEEGKTLLELVIEQFEDLLVRILLLAACISFVLAWFEEGE---ETITAFVEPFVI
ATC2_RABIT   1 -----------------------MENAHTKTVEEVLGHFGVNESTGLSLEQVKKLKERWGSNELPAEEGKTLLELVIEQFEDLLVRILLLAACISFVLAWFEEGE---ETITAFVEPFVI
ATC1_CHICK   1 -----------------------MENAHAKTAEECLAFFGVNESVGLSGEQVRRALEKYGHNELPAEEGKTIWELVVEQFEDLLVRILLLAACISFVLAWFEEGE---ETITAFVEPFVI
ATC1_HUMAN   1 -----------------------MEAAHAKTTEECLAYFGVSETTGLTPDQVKRNLEKYGLNELPAEEGKTLWELVIEQFEDLLVRILLLAACISFVLAWFEEGE---ETITAFVEPFVI
ATC1_RANES   1 -----------------------MEQAHTKTTEECLAYFGVNENTGLSLDQVKKNFDKFGPNELPAEEGKSLWELVAEQFEDLLVRILLLAAIISFVLAWFEEGE---ETVTAFVEPFVI
ATC1_MAKNI   1 -----------------------MENAHTKSPAECLSYFGVNEHTGLSPDQFKKNLDKFGYNELPAEEGKSIWDLIVEQFEDLLVRILLLAACISFVLAWFEEGE---ETITAFVEPFVI
Q27779       1 ----------------------MLEEAYSCTVDDILKHYNTNTETGLTKRQIESSLKEYGYNELPPEENKPLWKLVLGQFDDLLVKILLLAAIISFVLAWFEDSE---DATTAFVEPVVI
Q9SWS8       1 -----------------------MEDAYARSVSEVLDFFGVDPTKGLSDSQVVHHSRLYGRNVLPEEKRTPFWKLVLNSFDDLLVKILIVAAIVSFVLALANGET----GLTAFLEPFVI
ATC1_DUNBI   1 MVSHASSGRPSSRDTGMVYLGLGMQDAYSSEVQEVAAFYHVDLDRGLSDRDVQQARIKYGRNQMEAEQSTPLWKLILKQFDDLLVKILLGAAIVDFIIAISEGES----IQSGLIEPMVI
Q9UUY0       1 -----------------------MEAAFAKPVDEVLSTFGVDPTTGLSDEQVAQSRAKYGRNAIPEEPPTPIWELILEQFKDQLVLILLGSAAISFVLALFEDEG----GWSAFVDPAVI
AAF73985     1 ----------------------------------------------------MPAQAHNTSNLALISSDERGTRLLDQFEDTLVRVLVAAAAVSFLLALSSS--AGTLTLAAFVEPLVI
BAA90510     1 -MGEAGQDAPPPP---EKGVEVEVFPAWARGVEECEARLGVSASRGLSSREAAARLRAHGPNELAEHPGPTLLQLVAQQFDDTLVRILLAAAAVSFALALSSS--AGAVTLSAFVEPLVI
O04987       1 -MGKGSEDLVKKESLNSTPVNSDTFPAWAKDVAECEEHFVVSREKGLSSDEVLKRHQIYGLNELEKPEGTSIFKLILEQFNDTLVRILLAAAVISFVLAFFDGDEGGEMGITAFVEPLVI
O23087       1 -----------------MEEEKSFSAWSWSVEQCLKEYKTRLDKGLTSEDVQIRRQKYGFNELAKEKGKPLWHLVLEQFDDTLVKILLGAAFISFVLAFLGEEHGSGSGFEAFVEPFVI
Q42883       1 -----------------MEE-KPFPAWSWSVDQCLKEYQVKLEKGLSTYEVDKRRERYGLNELEKEKGKPLWRLVLEQFDDTLVKILLGAAFISFVLAYVNQDETGESGFEAYVEPLVI
consensus    1                        '' ''''''''''  '''     ''' '''     ''' '''' ''''''' '''''F'D'LV''L'''A'''F'''''' '      '''''''P''I
```

Figure 2 contd.

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O96608        98 LLILVLNATVGVWQENRAESAIEALK-SFVPKTAVVLREGK--LVTVGAENLVPADIVEVSVGNRVPADMRVLELHST-TLRADQAILNGESVEAIKEADAAIG---HQDRFPSSMVYSG
ATC_TRYBB     98 LLILILNATVGVWQENRAEGAIEALK-SFVPKTAVVLRDGD--IKTVNAEELVPGDVVEVAVGNRVPADMRVVELHST-TLRADQSILNGESVEAMKQIEAVKG---RQERFPACMVYSG
O09489       111 LLILTLNAIVGVWQEDRAEKAIDALKTSFLKQLLLFVR------VCRWQENLVPGDIVEVAVGDRVAADVRLLTLEST-TLRVDQSILNGESVEAMKQVESVRG---NRERFPSSMVYRG
O77070        94 LTILICNAVVGVWQEKNAEDAIEALK-EYEPEIAKVVRKGHRGVQKIRASLLVPGDIVEISVGDKIPADVRILQIYST-TLRIDQSILTGESVSVIKHTDPIPD-PRAVNQDKKNILFSG
O96039        94 LTILICNAVVGVWQEKNAEDAIEALK-EYEPEIAKVVRKGQRGVQKIRASLLVPGDIVEISVGDKIPADIRILHIYST-TLRIDQSILTGESVSVIKHTDPIPD-PRAVNQDKKNILFSG
O96696        95 LLILIANAVVGVWQERNAESAIEALK-EYEPEMGKVIRGDKSGVQKIRAKEIVPGDVVEVSVGDKIPADIRLIKIYST-TIRIDQSILTGESVSVIKHTDPIPD-PRAVNQDKKNILFSG
ATC1_DROME    95 LLILIANAVVGVWQERNAESAIEALK-EYEPEMGKVVRQDKSGIQKVRAKEIVPGDLVEVSVGDKIPADIRITHIYST-TLRIDQSILTGESVSVIKHTDAIPD-PRAVNQDKKNILFSG
O17314        95 LLILIANAIVGVWQERNAESAIEALK-EYEPEMGKVVRSNKHGVQKVRAREIVPGDIVEVSVGDKIPADIRLVKIFST-TLRIDQSILTGESVSVIKHADAIPD-PKAVNQDKKNILFSG
Q9XTG6        97 LLILIANATVGVWQERNAESAIEALK-EYEPEMAKVIRSGHHGIQMVRAKELVPGDLVEVSVGDKIPADLRLVKIYST-TIRIDQSILTGESVSVIKHTDSVPD-PRAVNQDKKNCLFSG
O96527        95 LLILIANAVIGVWQERNAESAIEALK-EYEPEIAKVFRKSHYGIQRIKARELVPGDIVEVSVGDKVPADMRIIKIMST-TLRVDQSILTGESVSVIKFTDAVPD-PRAVNQDKKNILFSG
O60900        95 MLILVANAIVGVWQERNAESAIEALK-EYEPEMGKVIRSDRKGVQRIRARDIVPGDIVEVAVGDKVPADLRLIEIKST-TLRVDQSILTGESVSVTKHTEAIPD-PRAVNQDKKNMLFSG
Q64517        95 MLILVANAIVGVWQERNAESAIEALK-EYEPEMGKVIRSDRKGVQRIRARDIVPGDIVEVAVGDKVPADLRLIEIKST-TLRVDQSILTGESVSVTKHTDAIPD-PRAVNQDKKNMLFSG
Q9YGL9        95 IMILIANAVVGVWQERNAESAIEALK-EYEPEMGKVIRADRSGVQRIRARDIVPGDIVEVAVGDKVPADIRIIEIRST-TLRVDQSILTGESMSVIKHADPIPD-PRAVNQDKKNMLFSG
ATC2_MOUSE    95 LLILVANAIVGVWQERNAENAIEALK-EYEPEMGKVYRQDRKSVQRIKAKDIVPGDIVEIAVGDKVPADIRLTSIKST-TLRVDQSILTGESVSVIKHTDPVPD-PRAVNQDKKNMLFSG
ATC2_RABIT    95 LLILVANAIVGVWQERNAENAIEALK-EYEPEMGKVYRQDRKSVQRIKAKDIVPGDIVEIAVGDKVPADIRLTSIKST-TLRVDQSILTGESVSVIKHTDPVPD-PRAVNQDKKNMLFSG
ATC1_CHICK    95 LLILIANAVVGVWQERNAENAIEALK-EYEPEMGKVYRADRKAVQRIKARDLVPGDIAEVAVGDKVPADIRIISIKST-TLRVDQSILTGESVSVIKHTEPVPD-PRAVNQDKKNMLFSG
ATC1_HUMAN    95 LLILIANAIVGVWQERNAENAIEALK-EYEPEMGKVYRADRKSVQRIKARDIVPGDIVEVAVGDKVPADIRILAIKST-TLRVDQSILTGESVSVIKHTEPVPD-PRAVNQDKKNMLFSG
ATC1_RANES    95 LLILIANAVVGVWQERNAEDAIEALK-EYEPEMGKVYRSDRKSVQRIKARELVPGDIVEVAVGDKVPADIRLISIKST-TLRIDQSILTGESVSVIKHTEVVPD-TRAVNQDKKNMLFSG
ATC1_MAKNI    95 LLILIANAIVGVWQERNAEDAIEALK-EYEPEMGKVYRSDRKSVQRIKAREIVPGDIVEVSVGDKVPADIRIVSIKST-TLRVDQSILTGESVSVIKHTESVPD-PRAVNQDKKNMLFSG
Q27779        96 MLILIVNAIVGVWQERNAESAIEALK-EYESDTAKVVRQGYQGVQSVKARELVPGDIVEVAVGDRVPADIRIVKILST-TLLIDQSILTGESVSVSKHSDPISQ-ARAVNQDKKNMLFSG
Q9SWS8        94 LLILAANAAVGVITETNAEKALEELR-AYQANIATVLRNGC--FSILPATELVPGDIVEVTVGCKIPADLRMIEMSSN-TFRVDQAILTGESCSVEKDVDCTLT-TNAVYQDKKNILFSG
ATC1_DUNBI   117 LLILVANATVGVVTERNAEKAIEQLK-SYEADDATVLRNGQ--LQLIPSADIVPGDIVELAVGNKVPADTRVSHIYTT-SLKIDQSLLTGESQAVEKHTEVVHN-EQAVYQDKLNMLFSG
Q9UUY0        94 ITILVLNAVVGVSQESSAEKAIAALQ-EYSANEANVVRNGQ--ITRIKAEDLVPGDVVDIAVGARVPADCRLISIESN-SFAVDQAILTGESESVGKDFQAVVSDDKAVLQDQVNMLFSG
AAF73985      66 FLILVVNAAVGVWQEANAERRVDALR-EIQSHHAAVLRDARCVPRAPLARDLVPGDVVQLRVGAKVPADMRVPASRAPPSSASSRASLTGETASVNKTSRALPL-EDADIQAKDCMVFAG
BAA90510     115 FLILVVNAAVGVWQETNAEKALEALR-EIQSDHAAVLRDGDWLPSLP-ARDLVPGDIVQLRVGDKVPADMRVLRLVTS-TLRVEQGSLTGETASVNKTAHQVPH-DDADIQAKECMVFAG
O04987       120 FLILIVNAIVGIWQETNAEKALEALK-EIQSQQATVMRDGTKVSSLP-AKELVPGDIVELRVGDKVPADMRVVALISS-TLRVEQGSLTGESEAVSKTTKHVD--ENADIQGKKCMVFAG
O23087       103 VLILILNAVVGVWQESNAEKALEALK-EMQCESAKVLRDGNVLPNLP-ARELVPGDIVELNVGDKVPADMRVSGLKTS-TLRVEQSSLTGEAMPVLKGANLVVM-DDCELQGKENMVFAG
Q42883       102 LWILVLNAIVGVWQESNAEKALEALK-EMQGESAKVLRDGYLVPDFP-AKELVPGDIVELRVGDKVPADMRVATLKSS-TLRVEQSSLTGESMPVTKSTDFLAT-DDCELQAKENMVFAG
consensus    121 ''IL''NA''G'''E''AE ''''L' ''''''''''R ''  ''''''''VP'D'''' VG''''AD'R'' ' '' ''''''''L'GE''''K''' ''' ''''''''''''''G
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Figure 2 contd.

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O96608      211 TSIVYGKAQCVVVRTGAFTEIGSIERDVREQ--EEVKTPLQIKLDEFGMLLSKVIGYTCLAVFVINMVRWYSVHTPTPD-EPWYERFIAPAIHCLKVAIALAVAAIPEGLPAVVTTCLAL
ATC_TRYBB   211 TAIVYGKALCVVVRTGASTEIGTIERDVREQ--EEVKTPLQVKLDEFGVLLSKVIGYICLVVFAVNLVRWYATHKPTKN-ETFFTRYIQPSVHCLKVAVALAVAAIPEGLPAVVTTCLAL
O09489      221 TAVVYGKARGVVVRTGTSTEMGFIERDVREQ--EETKTPLQLKLDEFGVLLSGVIGYICLFVFVANLLHWFRTHTPTTE-ESWFERYIQPTVHSLKVAVALAVAAIPEGLPAVVTTCLAL
O77070      211 TNISAGKCKGIAIGTGLNTAIGKIRDEMMET--ETEKTPLQQKLDEFGTQLSKVITIICICVWAINIGHFNDPAHGGS--------WMKGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
O96039      211 TNISAGKCKGIAFGTGLNTAIGKIRDEMMET--ETEKTPLQQKLDEFGTQLSKVITIICICVWAINIGHFNDPAHGGS--------WMKGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
O96696      212 TNVAAGKARGIVIGTGLNTAIGKIRTEMSET--EEIKTPLQQKLDEFGEQLSKVISVICVAVWAINIGHFNDPAHGGS--------WIKGAVYYFKIAVALAVAAIPEGLPAVITTCLAL
ATC1_DROME  212 TNVAAGKARGVVIGTGLSTAIGKIRTEMSET--EEIKTPLQQKLDEFGEQLSKVISVICVAVWAINIGHFNDPAHGGS--------WIKGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
O17314      212 TNVSAGKARGVVIGTGLATAIGKIRTQMAET--EEIKTPLQQKLDEFGEQLSKVISIICVAVWAINIGHFNDPAHGGS--------WIKGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
Q9XTG6      214 TNVASGKARGIVFGTGLTTEIGKIRTEMAET--ENEKTPLQQKLDEFGEQLSKVISVICVAVWAINIGHFNDPAHGGS--------WVKGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
O96527      212 TNIAAGKARGIVVSTGLMTEIGKIRNQMMDT--EPDKTPLQQKLDEFGQQLSKVISIICVAVWAINIGHFNDPAHGGS--------WLKGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
O60900      212 TNITSGKAVGVAVATGLHTELGKIRSQMAAV--EPERTPLQRKLDEFGRQLSHAISVICVAVWVINIGHFADPAHGGS--------WLRGAVYYFKIAVALAVAAIPEGLPAVITTCLAL
Q64517      212 TNIASGKALGVAVATGLQTELGKIRSQMAAV--EPERTPLQRKLDEFGRQLSHAISVICVAVWVINIGHFADPAHGGS--------WLRGAVYYFKIAVALAVAAIPEGLPAVITTCLAL
Q9YGL9      212 TNIAAGKAVGIVIATGVYTEIGKIRNQMVET--EPEKTPLQQKLDEFSQQLSKVIFLVCIAVWVINISHFSDPVHGGS--------WFRGAIYYFKTSVALAVAAIPEGLPAVITTCLAL
ATC2_MOUSE  212 TNIAAGKAMGVVVATGVNTEIGKIRDEMVAT--EQERTPLQQKLDEFGEQLSKVISLICIAVWIINIGHFNDPVHGGS--------WIRGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
ATC2_RABIT  212 TNIAAGKAMGVVVATGVNTEIGKIRDEMVAT--EQERTPLQQKLDEFGEQLSKVISLICIAVWIINIGHFNDPVHGGS--------WIRGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
ATC1_CHICK  212 TNIGAGKAVGIVVATGVNTEIGKIRDEMAAT--EQDKTPLQQKLDEFGEQLSKVISLICVAVWLINIGHFNDPVHGGS--------WIRGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
ATC1_HUMAN  212 TNIAAGKALGIVATTGVGTEIGKIRDQMAAT--EQDKTPLQQKLDEFGEQLSKVISLICVAVWLINIGHFNDPVHGGS--------WFRGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
ATC1_RANES  212 TNVGAGKAVGVVIATGPNTEIGKIRDEMAAT--EQEKTPLQQKLDEFGEQLSKVISLICVAVWLINIGHFNDPIHGGS--------WIKGAIYYFKIAVALAVAAIPEGLPAVITTCLAL
ATC1_MAKNI  212 TNIAAGKAIGVAIATGVSTEIGKIRDQMAAT--EQEKTPLQAKLDEFGEQLSKVISLICVAVWAINIGHFNDPVHGGS--------WIRGAVYYFKIAVALAVAAIPEGLPAVITTCLAL
Q27779      213 TNVASGKCVGIVVGTGLSTEIGKIRDQIMHT--EQDKTPLGQKIDEFGTQLSKVITFICIAVWCINIGHFNDPVHGGS--------WLRGAVYYFKIAVALAVAAIPEGLPAVITTCLAL
Q9SWS8      209 TDVVAGRGRAVVIGVGSNTAMGSIHDSMLQT--DDEATPLKKKLDEFGSFLAKVIAGICVLVWVVNIGHFSDPSHGG---------FFKGAIHYFKIAVALAVAAIPEGLPAVVTTCLAL
ATC1_DUNBI  232 TLVVAGRARGIVVGTGSNTAIGKIRDAMGVE--EDVVTPLKAKLDEFGALLSKVIAGICVLVWVVNINRFNDPALGG---------WFQGAIHYFKIAVALAVAAIPEGLPAVVTTCLAL
Q9UUY0      210 TTVVTGHAKAVVVLTGSNTAIGDIHESITAQ--ISEPTPLKQKLNDFGDQLAKVITVICVLVWLINIPNFADPSHGN---------WTKGAIYYLKIAVSLGVAAIPEGLAVVITTCLAL
AAF73985    184 TTVVNGAALCIVARTGMDTEIGAIHAQIHQASQEDDDTPLKKKLNEFGEALTKIIGLICALVWLINCKYFLTFDLQGGWVPRNITFSFEKCTYYFEIAVALAVAAIPEGLPAVITTCLAL
BAA90510    231 TTVVNGSAICLVVHTGMATEIGKIHAQIHEAAQEDDDTPLKKKLNEFGEALTKIIGLICALVWLINVKYFLTFELDG-WMPRNIRFSFEKCTYYFEIAVALAVAAIPEGLPAVITTCLAL
O04987      235 TTVVNGNCICLVTDTGMNTEIGRVHSQIQEAAQHEEDTPLKKKLNEFGEVLTMIIGLICALVWLINVKYFLSWEYVD-GWPRNFKFSFEKCTYYFEIAVALAVAAIPEGLPAVITTCLAL
O23087      219 TTVVNGSCVCIVTSIGMDTEIGKIQRQIHEASLEESETPLKKKLDEFGSRLTTAICIVCVLVWMINYKNFVSWDVVDGYKPVNIKFSFEKCTYYFKIAVALAVAAIPEGLPAVITTCLAL
Q42883      218 TTVVNGSCICIVVNTGMCTEIGKIQRQIHDASMEESDTPLKKKLDEFGNRLTFAIGVVCLVVWAINYKYFLSWEVVDDW-PSDFRFSFEKCAYYFKIAVALAVAAIPEGLPSVITTCLAL
consensus   241 T'' 'G'''''''''G' T''G'''  ' ''  ' ''TPL''K'''F'''L'''I'''C''V'''N''''''' ''''         ''''''''''''''L'VAAIPEGL''V'TTCLAL
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Figure 2 contd.

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                                      10
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O96608       328 GTRRMARHNALVRDLPSVETSAGGTVIWSDKTGTLTTDMMSVMEIFTLGLDG--------NPREYELKDSRFNVMPNVVTCGGKPVTSALETDGALSMLTNIAVLCNDASLHYNTTNGQV
ATC_TRYBB    328 GTRRMAQHNALVRDLPSVETLGRCTVICSDKTGTLTTNMMSVLHAFTLKGDG--------SIKEYELKDSRFNIVSNSVTCEGRQVSSPLEQDGALTKLANIAVLCNDASLHHNAATVQV
O09489       338 GARKMARHNALVRDLPSVETLGRCTVICSDKTGTLTTNMMSVSEVVTMEPSG--------KAHEYCLHDSRFNVVAASVSHRGTPAGDVLGNDAALDMVATIATLCSDASLIFGTRSAEV
O77070       321 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCKMFVFNKVE--GNGI--QTQQFEITGSTYAPEG-DVYLGGKKVK--TCDYEGLEEMATICAMCNDSSVDYNDTKGLY
O96039       321 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCKMFVFNKVE--GADI--QTQQFEITGSTYAPEG-DVYLGGKKVK--TCDYDGLEEMATICAMCNDSSVDYNDTKGVY
O96696       322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVSRMFIFEKIE--GGDS--SFLEFEITGSTYEPIG-DVYLKGQKIK--AAEFDALHELGTICVMCNDSAIDFNEFKQAF
ATC1_DROME   322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVSRMFIFDKVE--GNDS--SFLEFEMTGSTYEPIG-EVFLNGQRIK--AADYDTLQELSTICIMCNDSAIDYNEFKQAF
O17314       322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVSRMFIMDKVE--GNDS--SLLEFEVTGSTYEPIG-DVYLKNTKVK--GSDFEGLQELSTISFMCNDSSIDFNEFKNVF
Q9XTG6       324 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVSKMFIAGQAS--GDNI--NFTEFAISGSTYEPVG-KVSTNGREINPAAGEFESLTELAMICAMCNDSSVDYNETKKIY
O96527       322 GTRRMAAKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCRMFIFSKAD--DKAP--EVHHFEITGSKYAPEG-EVFLNGQKVE--SGEYDGLVEVANICAMCNDSAIDYNETKHVY
O60900       322 GTRRMARKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCRMFVVAEAD--AGSC--LLHEFTISGTTYTPEG-EVRQGDQPVR--CGQFDGLVELATICALCNDSALDYNEAKGVY
Q64517       322 GTRRMARKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCRMFVVAEAE--AGTC--RLHEFTISGTTYTPEG-EVRQGEQPVR--CGQFDGLVELATICALCNDSALDYNEAKGVY
Q9YGL9       322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCRMFIMEKVE--GTQC--SLHEFSITGSTYAPEG-QILKDEKPVR--CGQYDGLVELATICALCNDSSLDYNESKKVY
ATC2_MOUSE   322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCRMFILDKVE--GDTC--SLNEFSITGSTYAPIG-EVQKDDKPVK--CHQYDGLVELATICALCNDSALDYNEAKGVY
ATC2_RABIT   322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCRMFILDKVD--GDTC--SLNEFTITGSTYAPIG-EVHKDDKPVK--CHQYDGLVELATICALCNDSALDYNEAKGVY
ATC1_CHICK   322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCKMFIVDKVE--GDVC--SLNEFSITGSTYAPEG-DVLKNEKHIK--AGQHDGLVELATICALCNDSSLDYNEAKGIY
ATC1_HUMAN   322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCKMFIIDKVD--GDIC--LLNEFSITGSTYAPEG-EVLKNDKPVR--PGQYDGLVELATICALCNDSSLDFNEAKGVY
ATC1_RANES   322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMSVCRMFVIDKVE--GDVT--SLNEFTITGSTYAPEG-DVQKNDKNVK--AGQYDGLVELATICALCNDSSLDFNESKGVF
ATC1_MAKNI   322 GTRRMAKKNAIVRSLPSVETLGCTSVICSDKTGTLTTNQMCVTKMFIVKSVD--GDHV--DLNAFDISGSKYTPEG-EVSHGGSKTN--CSAYDGLVELATICALCNDSSLDYNESKKIY
Q27779       323 GTRRMARKNAIVRSLPSVETLGCTTVICSDKTGTLTTNQMTVCRMFTFGNESRIGDALQLKFDEFEITGSKYAPEG-NVHHQGRKVD--CSEYPCLVELAQICSLCNDSSMEYNESRHAY
Q9SWS8       318 GTKKMARLNAIVRSLPSVETLGCTTVICSDKTGTLTTNMMSVSKICVVQSAE--HG-P--MINEFLLVETTYAPEG-TVFDSNGMQLDLPAQSPCLHHLAMCSSLCNDSILQYNPDKDSY
ATC1_DUNBI   341 GTRKMARHNAIVRTLPSVETLGCTTVICSDKTGTLTTNQMSVIKVAAVQSSS--S-----QLAEFDVTGTTFSPEG-MVLGPGGVVLRQPADTPCLAHAAQCAALCNDSQVFVAQKTGTL
Q9UUY0       319 GTRKMAAKNAVVRSLPSVETLGSCSVICSDKTGTLTTNQMSVNKIVHFNQDG--T-----DLEELDVEGTTFEPKG-AIMSQGKKVTDLAQNSATILQLTEVAALCNDARLDYHPSTGTF
AAF73985     304 GTRKMAAKNALVRKLPSVETLGCTTVICSDKTGTLTSNKMSVAKLVAVGDSS----Q---EVRTFKVDGTTYDPRD-----GKIHDWPAGSIDANLETIAKVAAVCNDANVAHSS--HQY
BAA90510     350 GTRKMAAKNALVRKLPSVETLGCTTVICSDKTGTLTTNQMSVAKLVAIGDAE----G---KVRSFKVDGTTYDPRD-----GRIHDWPAGRMDANLQTIAKISAVCNDASVAHSS--HQY
O04987       354 GTRKMAQKNALVRKLPSVETLGCTTVICSDKTGTLTTNQMAVSKLVAMGSRI----G---TLRSFNVEGTSFDPRD-----GKIEDWPMGRMDANLQMIAKIAAICNDANVEQSD--QQF
O23087       339 GTRKMAQKNAIVRKLPSVETLGCTTVICSDKTGTLTTNQMSATEFFTLGGKT----T---TTRVFSVSGTTYDPKD-----GGIVDWGCNNMDANLQAVAEICSICNDAGVFYEG--KLF
Q42883       337 GTRKMAQKNAIVRKLQSVETLGCTTVICSDKTGTLTTNQMSVSEFFTLGRKT----T---ACRVFGVEGTTYDPKD-----GGIMNWNCCKMDANLLLMAEICAICNDAGVFCDG--RLF
consensus    361 G''MA''NA'VR'L'SVET''''VI'SDKTGTLT''M'' '''''  '  '   ' '' '''''' ' ' ''  ' '   '''' '''''''C'D'''''' ' ''
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Figure 2 contd.

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O96608       440 EKIGEATEAALLVMSEKLAHAT-----------DPTAVC--------AFRKLAEQKWKKNTTLEFTRQRKSMSEHATSTAG------------AKLNSLFVKGAPEEVLRRSTHVMQV--
ATC_TRYBB    440 EKIGEATEAALLVMSEKFANIK-----------GDSAVN--------AFRTLCEGKWKKNATLEFTRKRKSMSVHVTSTVTGSP--------ASSTNNLFVKGAPEEVLRRSTHVMQD--
O09489       450 EKVGDATEAALLVMSEKLYHSA-----------AWNGVDGAR-LPADRCRSLKKKLWLKKATLEFTRSRKSMSVCCTSTRH-------------SL---FVKGAPEEILKRCTRIMFK--
O77070       434 EKVGEATETALTVLCEKMNFFN----------TSRGGMSLRE-Q-GTVCNHVIQQMWSKEFTLEFSRDRKSMSVFCTPNKPTK----------VPGGSKMFAKGAPEGLLDRCTHVRVG--
O96039       434 EKVGEATETALTVLCEKMNFFN----------TGRSGLNLRE-Q-GTVCNHVIQQMWSKEFTLEFSRDRKSMSVYCTPNKPSK----------IPGGTNMFAKGAPEGLLDRCTHVRVG--
O96696       435 EKVGEATETALIVLAEKMNPFN----------VPKTGLDRRS-C-AIVVRQEIETKWKKEFTLEFSRDRKSMSTYCTPLKPSR----------LGNGPKLFVKGAPEGVLERCTHARVG--
ATC1_DROME   435 EKVGEATETALIVLAEKLNSFS----------VNKSGLDRRS-A-AIACRGEIETKWKKEFTLEFSRDRKSMSSYCTPLKASR----------LGTGPKLFVKGAPEGVLERCTHARVG--
O17314       435 EKVGEATETALIVLGEKINPYN----------MSKSGLDRRS-A-AIIARHDMETKWKKEFTLEFSRDRKSMSSYCVPLKPTR----------LGTGPKMFCKGAPEGVLDRCTHVRVG--
Q9XTG6       439 EKVGEATETALIVLAEKMNVFG----------TSKAGLSPKE-L-GGVCNRVIQQKWKKEFTLEFSRDRKSMSAYCFPASG------------GSGAKMFVKGAPEGVLGRCTHVRVN--
O96527       435 EKVGEATETALCCLVEKMNVYK----------TSKSGLSKKD-L-SMVCNHQIQAMWNKEFTLEFSRDRKSMSVYLQVKPAFASKVPNTAGSGETGPRMFVKGAPEGVLDRCTFVRIG--
O60900       435 EKVGEATETALTCLVEKMNVFD----------TDLQALSRVE-R-AGACNTVIKQLMRKEFTLEFSRDRKSMSVYCTPTRPHP----------TGQGSKMFVKGAPESVIERCSSVRVG--
Q64517       435 EKVGEATETALTCLVEKMNVFD----------TDLKGLSRVE-R-AGACNSVIKQLMRKEFTLEFSRDRKSMSVYCTPTRADP----------KVQGSKMFVKGAPESVIERCSSVRVG--
Q9YGL9       435 EKVGEATETALTCLVEKMNVFD----------TDTSKLSKVE-R-ANACNSVIKHLMRKECTLEFSRDRKSMSVYCTPTGPGH----------NSAGSKMFVKGAPESVIERCTHVRVG--
ATC2_MOUSE   435 EKVGEATETALTCLVEKMNVFD----------TELKGLSKIE-R-ANACNSVIKQLMKKEFTLEFSRDRKSMSVYCTPNKPSR----------TSMS-KMFVKGAPEGVIDRCTHIRVG--
ATC2_RABIT   435 EKVGEATETALTCLVEKMNVFD----------TELKGLSKIE-R-ANACNSVIKQLMKKEFTLEFSRDRKSMSVYCTPNKPSR----------TSMS-KMFVKGAPEGVIDRCTHIRVG--
ATC1_CHICK   435 EKVGEATETALTCLVEKMNVFN----------TDVRSLSKVE-R-ANACNSVIKQLMKKEFTLEFSRDRKSMSVYCSPAKASR----------AAVGNKMFVKGAPEGVIDRCNYVRVG--
ATC1_HUMAN   435 EKVGEATETALTTLVEKMNVFN----------TDVRSLSKVE-R-ANACNSVIRQLMKKEFTLEFSRDRKSMSVYCSPAKSSR----------AAVGNKMFVKGAPEGVIDRCNYVRVG--
ATC1_RANES   435 EKVGEATETALTTLVEKMNVFN----------TDVKSLSKVE-R-ANACNSVIKQLMKKEFTLEFSRDRKSMSVYCIPAKASR----------AAVGNKMFVKGAPEGVIDRCNYVRVG--
ATC1_MAKNI   435 EKVGEATETALCCLVEKMNVFN----------SNVKNLSRIE-R-ANACCTVIKQLMKKNFTLEFSRDRKSMSVYCTPAK------------GDGGAKMFVKGAPEGVIDRCAYVRVG--
Q27779       440 EKVGEATETALVCLVEKMNVTK----------VSKSNLTNHQ-L-AMVCNRDIQKMFERKFTLEFSRDRKSMSTYVIPQSQIS----------GSKEKLFVKGAPESILDRCTYVRTA--
Q9SWS8       432 EKIGESTEVALRVLAEKVGLPGFDS-----MPSALNMLSKHE-R-ASYCNHYWENQFKKVYVLEFTRDRKMMSVLCS-HKQMD--------------VMFSKGAPESIIARCNKILCN-G
ATC1_DUNBI   453 QRIGESTEIALRVFAEKIGLP---S-----SIRPDRPISRSQ----FGTNNFWQEDVERLALLEFSRDRKMMSVLVKGSDRQH-------------NIWSKGAPEFVLRKCSHVLANNG
Q9UUY0       431 SNVGEATEGALRVLTEKIGPC---------APSDCPPKDRVH-----YASSWYEKQYQRLATYEFSRDRKSMSVLVE-RDGQQ--------------KLLVKGAPESLIERCTHALLG-P
AAF73985     410 VATGMPTEAALKVLVEKMGLPGGKN------------GLSLDP-SEILGCCAWWNNVAKRIATLEFDRTRKSMGVVVKTSSGSN--------------ALLVKGAVETLLERSSHIQLK--
BAA90510     456 TATGMPTEAALKVLVEKMGIPEGMN------------GLSLDP-SETLGCCQWWSNVAKRIATLEFDRTRKSMGVIVKSKSGRN--------------ALLVKGAVENLLERSSHIQLQ--
O04987       460 VSRGMPTEAALKVLVEKMGFPEGLN-----------EASSD--GDVLRCCRLWSELEQRIATLEFDRDRKSMGVMVDSSSGNK--------------LLLVKGAVENVLERSTHIQLL--
O23087       445 RATGLPTEAALKVLVEKMGIPEKKN---SENIEEVTNFSDNGSSVKLACCDWWNKRSKKVATLEFDRVRKSMSVIVSEPNGQN--------------RLLVKGAAESILERSSFAQLA--
O42883       443 KATGLPTEAALKVLVEKMGVPDSKARCKIRDAQIVSSYLIDRNTVKLGCCDWWMKRSKRVATLEFDRVRKSMGVIVREPNGSN--------------RLLVKGAFESLLERSTYVQLA--
consensus    481 '''G''TE'AL '''EK''''           '    '''' '   ' ''' '' '' ''''''EF'R'RK'M'''''' '              ' ''''KGA'E ''''''''''
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Figure 2 contd.

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O96608      527 DGVVIPLSDALRSRIIAEIDAMSGSEHALRCIGFAFKSTQ---------PV--RELKLSDPSTFEQIESDLTFVGACGMLDPPRAEVREAIDNCRTAGIRVVVITGDRKETAEAICRKLG
ATC_TRYBB   531 NGAVVQLSATHRKRIIEQLDKISGGANALRCIGFAFKPTK---------AV--QHVRLNDPATFEDVESDLTFVGACGMLDPPREEVRDAIVKCRTAGIRVVVITGDRKETAEAICCKLG
O09489      540 DGRISPLTPKMVNTVTANIDRMSGTEEALRCIAFAFRPIP---------DP--KQLDLSDPAKFEAIDSHLTWGGVFGILDPPRREVADAIAKCRTAGIRVIVITGDKKETAEAVCRRIG
O77070      531 -KDKVPMSPAIKNEIMKYTKIYGTGRDTLRCLALATIDAP---------PR-REDMDLEDARKFIQYETNMTFVGVVGMLDPPRMEVFDSIKNCRKAGIRVIVITGDNKATAEAICRRIG
O96039      531 -KDKVPMSPAIKNEILKYTKAYGTGRDTLRCLALATIDAP---------PR-REDMDLEDSRKFIQYETNMTFVGVVGMLDPPRMEVFDSIKNCRKAGIRVIVITGDNKATAEAICRRIG
O96696      532 -TAKVPLNSTLKNRILDLTRQYGTGRDTLRCLALATADSP---------LK-PDEMDLGDSTKFYTYEVNLTFVGVVGMLDPPRKEVFDSIVRCRAAGIRVIVITGDNKATAEAICRRIG
ATC1_DROME  532 -TTKVPLTSALKAKILALTGQYGTGRDTLRCLALAVADSP---------MK-PDEMDLGDSTKFYQYEVNLTFVGVVGMLDPPRKEVFDSIVRCRAAGIRVIVITGDNKATAEAICRRIG
O17314      532 -TQKVPLTAGVKEKILSVTRDYGCGRDTLRCLGLATIDNP---------MK-PEDMDLGEASKFYTYEVNMTFVGVVGMLDPPRKEVKDSIQRCRDAGIRVIVITGDNKATAEAICRRIG
Q9XTG6      533 -GQKVPLTSAMTQKIVDQCVQYGTGRDTLRCLALGTIDTP---------VS-VSNMNLEDSTQFVKYEQDITFVGVVGMLDPPRTEVSDSIKACNHAGIRVIMITGDNKNTAEAIGRRIG
O96527      541 -NKKVPMTPPLKAEIVKHVASYGTGRDTLRCLALATCDAP---------VN-KAQMDLEDSTKFVKYEQNLTFVGVVGMLDPPRMEVFDSIARCRKSGIRVIMITGDNKATAEAICRRIG
O60900      532 -SRTAPLTPTSREQILAKIRDWGSGSDTLRCLALATRDAP---------PR-KEDMELDDCSKFVQYETDLTFVGCVGMLDPPRPEVAACITRCYQAGIRVVMITGDNKGTAVAICRRLG
Q64517      532 -SRTAPLSTTSREHILAKIRDWGSGSDTLRCLALATRDTP---------PR-KEDMHLDDCSRFVQYETDLTFVGCVGMLDPPRPEVAACITRCSRAGIRVVMITGDNKGTAVAICRRLG
Q9YGL9      532 -TAKVPLTPPVREKILSQIRDWGMGTDTLRCLALATHDAP---------VQ-RETMQLHDSTTFTHYETNLTFVGCVGMLDPPRKEVTSSIEMCRKAGIRVIMITGDNKGTAVAICRRIG
ATC2_MOUSE  531 -STKVPMTPGVKQKIMSVIREWGSGSDTLRCLALATHDNP---------LK-REEMHLEDSANFIKYETNLTFVGCVGMLDPPRIEVASSVKLCRQAGIRVIMITGDNKGTAVAICRRIG
ATC2_RABIT  531 -STKVPMTAGVKQKIMSVIREWGSGSDTLRCLALATHDNP---------LR-REEMHLKDSANFIKYETNLTFVGCVGMLDPPRIEVASSVKLCRQAGIRVIMITGDNKGTAVAICRRIG
ATC1_CHICK  532 -TTRVPLTPAVKEKILAVIKEWGTGRDTLRCLALATRDTP---------PK-MEDMMLVDSTKFAEYETDLTFVGCVGMLDPPRKEVMGSIRLCRDAGIRVIMITGDNKGTAIAICRRIG
ATC1_HUMAN  532 -TTRVPLTGPVKEKIMAVIKEWGTGRDTLRCLALATRDTP---------PK-REEMVLDDSARFLEYETDLTFVGVVGMLDPPRKEVTGSIQLCRDAGIRVIMITGDNKGTAIAICRRIG
ATC1_RANES  532 -TTRVPLTSAIKDKILSVVKEWGTGRDTLRCLALATRDTP---------PK-REDMVLDEATRFIEYETDLTFVGCVGMLDPPRKEVMGSIQLCREAGIRVIMITGDNKGTAIAICRRIG
ATC1_MAKNI  529 -TTRVPLTSAIKEKIMAVIRDWGTGRDTLRCLALATRDTP---------LK-VEEMNLEDSTKFADYETDMTFVGCVGMLDPPRKEVTGSIELCRDAGIRVIMITGDNKGTAIAICRRIG
Q27779      536 -GGKLLLTSELKGEVLRKIATYATGRETLRCLALATRDEP---------P---SHFDLKDPKNFKDYETELTLVGVVGMVDPPRCEVASSIQACKKAGIRVIVITGDNKATAEAICRRIG
Q9SWS8      529 DGSVVPLTAAGRAELESRFYSFG--DETLRCLALAFKT----------------VPHGQQTISYD-NENDLTFIGLVGMLDPPREEVRDAMLACMTAGIRVIVVTGDNKSTAESLCRKIG
ATC1_DUNBI  547 EG-AVPLTDNMRQAILSDMQAFGS-RQALRCLALAFKS----------------VPTTTTKLDYS-DESGLTFIGLLGMHDPPRPECRSALSTCHNAGIKVIMVTGDNKGTAEAVARQVG
Q9UUY0      521 DGKKVPLDSNMSELLMKEVVEYG--NRGLRVIALASLDNV---------AGNPLLHTAKSTAEYASLEQNLTLIGLVGMLDPPRPEVAASIKKCKDAGIRVVVITGDNRNTAESICRQIG
AAF73985    502 DGSVVPLDEKAKRTILASLHEMS--TNALRCLGFAYKEALAEFRTYDG-ENHPRHNVFVDPANYAAIETDLIFAGLVGLRDPPREEVYDAIEDCRAAGIRVMVITGDNKETAEAICREIG
BAA90510    548 DGSVVPLDEKSRKAILENLHEMS--IKALRCLGFAYKEDLAEFASYDG-ENHPAHKLLLDPVNYAAIETNLIFTGLAGLRDPPREEVFDAIEDCRAAGIRVMVITGDNKETAEAICREIG
O04987      551 DGSKRELDQYSRDLILQSLRDMS--LSALRCLGFAYSDVPSDFATYDGSEDHPAHQQLLNPSNYSSIESNLIFVGFVGLRDPPRKEVRQAIADCRTAGIRVMVITGDNKSTAEAICREIG
O23087      546 DGSLVALDESSREVILKKHSEMT--SKGLRCLGLAYKDELGEFSDYSS-EEHPSHKKLLDPSSYSNIETNLIFVGVVGLRDPPREEVGRAIEDCRDAGIRVMVITGDNKSTAEAICCEIR
Q42883      547 DGSTVPLDESCRQLLLLKQLEMS--SKGLRCLGLAYKDDLGELSGYYA-ATHPAHKKLLDPSCYSSIESDLVFVGVVGLRDPPREEVHRAVNDCRRAGIKIMVITGDNKSTAEAVCREIQ
consensus   601     '''''  ''  ''  ''''''' ''LR''''''''  '              ''' ' ' ' '  ''' ''''G''G''DPPR E'  ''  C' 'GI''''TGD'''TA''''''''
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Figure 2 contd.

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O96608       636 LLLKT-ETSG--------LSYTGAEFEGMN--PAEKRKAVMSAVLFSRTDPSHKMQLVKLLQEQ---KLICARTGDGVN-DAPALKKADIGIAMG--SGTQVAKAASKMVLAEDNFATVV
ATC_TRYBB    640 LLSSTADTTG--------LSYTGQELDAMT--PAQKREAVLTAVLFSRTDPSHKMQLVQLLKDE---RLICAMTGDGVN-DAPALKKADIGIAMG--SGTEVAKSASKMVLADDNFATVV
O09489       649 LMSSE-PTKG--------LSFTGYELDQMT--PAQRRAAVSSAVLFSRTDPSHKMQLVNLLQEQ---KLICAMTGDGVN-DSPALKKADIGIAMG--SGTEVAKAASKLVLADDNFATVV
O77070       640 VFGENESTEG--------MSYTGREFDDLS--PEEQRLAVMKSRLFARVEPAHKSKIVEYLQGE---GEISAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSASEMVLADDNFATIV
O96039       640 VFGENESTEG--------MSFTGREFDDLS--HEEQRLAVTKSRLFARVEPAHKSKIVEYLQGE---GEISAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSASEMVLADDNFATIV
O96696       641 VFTEEEDTTG--------KSFSGREFDDLP--VSEQRAACAKARLFSRVEPAHKSKIVEFLQSM---NEISAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSAAEMVLADDNFSSIV
ATC1_DROME   641 VFAEDEDTTG--------KSYSGREFDDLS--PTEQKAAVARSRLFSRVEPQHKSKIVEFLQSM---NEISAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSAAEMVLADDNFSSIV
O17314       641 VFKEDEDTTG--------MSYSGREFDELS--PEEQRQACIRSRLFSRVEPFRKSKIVEYLQGE---NEISAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSASEMVLADDNFSSIV
Q9XTG6       642 LFGENEDTTG--------KAYTGREFDDLP--PEQQSEACRRAKLFARVEPSHKSKIVDILQSQ---GEITAMTGDGVN-DAPALKKAEIGISMG--SGTAVAKSASEMVLADDNFASIV
O96527       650 IFSEDEPTTG--------KSFTGREFDALP--IEEQREACRRARLFARVEPMHKSKIVEFLQED---GEVSAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSAADMVLADDNFNSIV
O60900       641 IFGDTEDVAG--------KAYTGREFDDLS--PEQQRQACRTARCFARVEPAHKSRIVENLQSF---NEITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSAAEMVLSDDNFASIV
Q64517       641 IFGDTEDVLG--------KAYTGREFDDLS--PEQQRQACRTARCFARVEPAHKSRIVENLQSF---NEITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSAAEMVLSDDNFASIV
Q9YGL9       641 IFTESEDVAG--------KAYTGREFDELS--PEAQRQACREARCFARVEPAHKSRIVEYLQSF---NEITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSAAEMVLSDDNFSTIV
ATC2_MOUSE   640 IFGQDEDVTS--------KAFTGREFDELS--PSAQRDACLNARCFARVEPSHKSKIVEFLQSF---DEITAMTGDGVN-DAPALKKSEIGIAMG--SGTAVAKTASEMVLADDNFSTIV
ATC2_RABIT   640 IFGQEEDVTA--------KAFTGREFDELN--PSAQRDACLNARCFARVEPSHKSKIVEFLQSF---DEITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKTASEMVLADDNFSTIV
ATC1_CHICK   641 IFTEDEEVSG--------RAYTGREFDDLP--PAEQREACRRACCFARVEPTHKSKIVEFLQSF---DEITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKTASEMVLADDNFSTIV
ATC1_HUMAN   641 IFGENEEVAD--------RAYTGREFDDLP--LAEQREACRRACCFARVEPSHKSKIVEYLQSY---DEITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKTASEMVLADDNFSTIV
ATC1_RANES   641 IFGEDDDVSG--------RAFTGREFDDLP--PAEQREACKRASCFARVEPAHKSKIVEFLQSF---DEITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKTASEMVLADDNFSTIV
ATC1_MAKNI   638 IFKEDEDVSN--------KAYTGREFDDLP--SQDQAEAVRRACCFARVEPSHKSKIVEFLQGN---DDITAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSASEMVLADDNFSSIV
Q27779       643 LFEDKEDTSG--------KSFTGREFDDLS--LEKKKDAVRNGKLFARVEPAHKSLIVQFLQQD---GEISAMTGDGVN-DAPALKKAEIGIAMG--SGTAVAKSASDMVLADDNFSTIV
Q9SWS8       630 AFDNLVDFSG--------MSYTASEFERLP--AVQQTLALRRMTLFSRVEPSHKRMLVEALQKQ---NEVVAMTGDGVN-DAPALKKADIGIAMG--SGTAVAKSASDMVLADDNFASIV
ATC1_DUNBI   648 ALSPSTALAGSDDEDNLGISYTGREFEEMG--ALGQAAATRNLVVLSRVEPMHKLRLVELLKAQ---GHVVAMTGDGVN-DAPALLRADIGIAMG--SGTAVAKHAADMVLGDDNFATIV
Q9UUY0       630 VEGSNEDLTG--------KSYTGREFDNLT--PSEQLEAAKTASLFSRVEPTHKSKLVDLLQSL---GEVVAMTGDGVN-DAPALKKADIGVAMG--SGTDVSKLAADMVLADDNFATIE
AAF73985     619 VFSPDEDITF--------KSLQGKEFMALE-DKKTARLPVKGGLLFSRAEPRQQTRTIRGGLAEGRIGQVVAMTGDGVNVSAPALKLVDIGVAMGVITGTEVAKEASDMVLADDNFSTIV
BAA90510     665 VFSHDEDITL--------KSLTGKEFMALE-DKKTLLR-RKGGLLFSRAEPRHKQEIVRLLKED---GEVVAMTGDGVN-DAPALKLADIGVAMG-ITGTEVAKEASDMVLADDNFSTIV
O04987       669 VFEADEDISS--------RSLTGIEFMDVQ-DQKNHLR-QTGGLLFSRAEPKHKQEIVRLLKED---GEVVAMTGDGVN-DAPALKLADIGVAMG-ISGTEVAKEASDMVLADDNFSTIV
O23087       663 LFSENEDLSQ--------SSFTGKEFMSLPASRRSEILSKSGGKVFSRAEPRHKQEIVRMLKEM---GEIVAMTGDGVN-DAPALKLADIGIAMG-ITGTEVAKEASDMVLADDNFSTIV
Q42883       664 LFSNGENLRG--------SSFTGKEFMAFSSQQQIEILSQDGGKVFSRAEPRHKQEIVRMLKEM---GEIVAMTGDGVN-DAPALKLADIGIAMG-ITGTEVAKEASDMVLADDNFSTIV
consensus    721 '' ' '''''        ''''''E''''   '  '' ' ' '''' R''P '''''''''      '''A'TGDGVN ''PAL''''IG''MG  'GT'V'K'A'''VL''DNF''''
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Figure 2 contd.

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O96608       739 KAVGEGRAIFNNTKQFIRYLISSNIGEVACILLTGLCGLPEALSPVQLLWVNLVTDGFPATAFGFNAPDEDIMQQPPR-HVDEPIVNGWMFLRYMVIGVYVGLATIGGFLWWFLSHG---
ATC_TRYBB    744 KAVQEGRAIYNNTKQFIRYLISSNIGEVVCILVTGLFGLPEALSPVQLLWVNLVTDGLPATALGFNAPDRDIMEQRPR-RMEEPIVNGWLFMRYMVIGVYVGLATVGGFLWWFLRHG---
O09489       752 KAVHEGRTIFNNTKQFIRYLISSNIGEVACVLATDCLAC-QKHSADQLLWVNLVTDGLPATACWVQTPPIQTLWNRHRGEETSPLSTGWLFFRYMVVGVYVGLATVAGFVWWFLTNG---
O77070       744 SAVEEGRAIYNNMKQFIRYLISSNIGEVVCIFLTAALGIPEALIPVQLLWVNLVTDGLPATALGFNPPDMDIMKKPPR-NAKEGLITGWLFFRYMAIGGYVGCATVGAAAWWFMVYDKG-
O96039       744 SAVEEGRAIYNNMKQFIRYLISSNIGEVVCIFLTAALGIPEALIPVQLLWVNLVTDGLPATALGFNPPDMDIMKKPPR-NAKEGLITGWLFFRYMAIGGYVGCATVGAAAWWFMVYDKG-
O96696       745 AAVEEGRAIYNNMKQFIRYLISSNIGEVVSIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDKPPR-KADEGLISGWLFFRYMAIGGYVGAATVGAASWWFMYSPFG-
ATC1_DROME   745 SAVEEGRAIYNNMKQFIRYLISSNIGEVVSIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMEKPPR-KADEGLISGWLFFRYMAIGFYVGAATVGAAAWWFVFSDEG-
O17314       745 AAVEEGRAIYNNMKQFIRYLISSNVGEVVSIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDKPPR-RADESLISGWLFFRYMAIGGYVGAATVFAASWWFMYDPTG-
Q9XTG6       746 SAVEEGRAIYNNMKQFIRYLISSNVGEVVSIFMVAALGIPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDRHPR-SANDGLISGWLFFRYLAVGTYVGVATVGASMWWFLLYEEG-
O96527       754 LAVEEGRAIYNNMKQFIRYLISSNIGEVVSIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMERPPR-NIKDPLISGWLFFRYVAIGVYVGCATVGAAAWWFSLYPKG-
O60900       745 AAVEEGRAIYSNMKQFIRYLISSNVGEVVCIFLTAILGLPEALIPVQLLWVNLVTDGHPATALGFNPPDLDIMEKLPR-SPREALISGWLFFRYLAIGVYVGLATVAAATWWFVYDAEG-
Q64517       745 AAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAILGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMEKPPR-NPREALISGWLFFRYLAIGVYVGLATVAAATWWFLYDAEG-
Q9YGL9       745 SAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAILGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDKLPR-NPKEPLISGWLFFRYLAIGVYVGLATVGAATWWFLYDAEG-
ATC2_MOUSE   744 AAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAALGFPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMNKPPR-NPKEPLISGWLFFRYLAIGCYVGAATVGAAAWWFIAADGG-
ATC2_RABIT   744 AAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAALGFPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMNKPPR-NPKEPLISGWLFFRYLAIGCYVGAATVGAAAWWFIAADGG-
ATC1_CHICK   745 AAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDKPPR-SPKEPLISGWLFFRYLAIGGYVGAATVGAAAWWFLYAEDG-
ATC1_HUMAN   745 AAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDRPPR-SPKEPLISGWLFFRYMAIGGYVGAATVGAAAWWFLYAEDG-
ATC1_RANES   745 AAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMDRPPR-SPKEPLISGWLFFRYMAIGGYVGAATVGAAAWWFMYADDG-
ATC1_MAKNI   742 AAVEEGRAIYNNMKQFIRYLISSNVGEVVCIFLTAALGLPEALIPVQLLWVNLVTDGLPATALGFNPPDLDIMGKPPR-SPKEPLISGWLFFRYMAIGGYVGAATVGGAAWWFLYDSTG-
Q27779       747 AAVEEGRAIYDNMKQFIRYLISSNIGEVVCIFLTAALGMPEALIPVQLLWVNLVTDGLPATALGFNPPDVDIMTKPPR-KSKEPLISGWLFLRYMLIGIYVGCATVGAAAWWFMVYEGG-
Q9SWS8       734 AAVAEGRAIYNNTRQFIRYMISSNIGEVVCIFVAAVLGIPDTLAPVQLLWVNLVTDGLPATAIGFNKQDSDVMKAKPR-KVGEAVVTGWLFFRYLVIGVYVGLATVAGFIWWFVYSDGG-
ATC1_DUNBI   760 FAVAEGRVIFNNTKQFIRYMISSNIGEVVAIFLAALLGLPEVLTPVQLLWVNLVTDGLPATALGFNRADKDMMARGPR-RVDDPIVNGWLFLRYLIIGMYVGIVTVYGFIWWYISFPEG-
Q9UUY0       734 VAIEEGRAIYNNTQQFIRYLISSNIGEVVSIFLTAALGMPEALIPVQLLWVNLVTDGLPATALSFNPPDHDIMRRNPR-KRDEALIGGWLFFRYLVIGTYVGLATVAGYAWWFMFYSEC-
AAF73985     730 SAVGEGRSIYNNMKAFIRYMISSNIGEVASIFLTSALGIPEGLIPVQLLWVNLVTDGPPATSLGFNPPDKDIMKKPPR-RSDDTLITPWILFRYLVIGLYVGMAT-GILLIWYTHGSFMG
BAA90510     770 AAVGEGRSIYNNMKAFIRYMISSNIGEVASIFLTSALGIPEGLIPVQLLWVNLVTDGPPATALGFNPPDKDIMKKPPR-KSDDSLITPWILFRYLVIGLYVGIATVGIFVIWYTHGSFMG
O04987       774 AAVGEGRSIYNNMKAFIRYMISSNIGEVASIFLTAALGIPEGMIPVQLLWVNLVTDGPPATALGFNPPDKDIMKKPPR-RSDDSLITAWILFRYMVIGLYVGVATVGVFIIWYTHSSFMG
O23087       770 SAVAEGRSIYNNMKAFIRYMISSNVGEVISIFLTAALGIPECMIPVQLLWVNLVTDGPPATALGFNPADIDIMKKPPR-KSDDCLIDSWVLIRYLVIGSYVGVATVGIFVLWYTQASFLG
Q42883       771 SAVAEGRSIYNNMKAFIRYMISSNVGEVISIFLTAVLGIPECLIPVQLLWVNLVTDGPPATALGFNPADVDIMQKPPR-KNTDALINSWVFFRYMVIGSYVGIATVGIFIVWYTQASFLG
consensus    841 'A''EGR'I''N'''FIRY'ISSN'GEV''''''''''''''''QLLWVNLVTDG'PAT''''''''''' '''R     ' ''''W'''RY'''G YVG''T'''' 'W''     '
                                <---------                  <--------
                                    12                          .9
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Figure 2 contd.

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O96608       855 ----------FNWKDLTTYAACTDM----------------QD-----AKCAILADP--ETARAIALSILVLVEMLNALNALSENASLITARPSSNIWLLLAIFSSLALHLMIMYVPFLAA
ATC_TRYBB    860 ----------FSWHDLTTYTACSDM----------------TN-----GTCLLLANP--QTARAIALSILVVVEMLNALNALSENASLIVSRPSSNVWLLFAIFSSLSLHLIIMYVPFFAK
O09489       868 ----------FTMADLVSFTTCTDM----------------SN-----PKCAVLANP--QTARAIALSILVVVEMLNALNALSENQSLVVIRPSTNKWLIAAICSSIALHLTIMYIPFFSR
O77070       862 ---------PQLNYYQLTHHMQCLAE---------------PK-MFPGIDCKIFGA---PEPMTMALSVLVTIEMLNALNSLSENQSLLVMPPWCNKWLLGAMALSNGLHFCILYIDIMST
O96039       862 ---------PQLNYYQLTHHSQCLAQ---------------DE-RFLGVDCKVFDH---PAPMTMALSVLVVIEMLNALNSLSENQSLLVMPPWCNKWLLGAMALSNGLHFCILYIDVMST
O96696       863 ---------PQMSYWQLTHHLQCLSG---------------GD-EFKGIDCKIFTD---PHPMTMALSVLVTIEMLNAMNSLSENQSLVTMPPWSNMWLVGSMALSFTLHFVILYVEVLSA
ATC1_DROME   863 ---------PKLSYWQLTHHLSCLGG---------------GD-EFKGVDCKIFSD---PHAMTMALSVLVTIEMLNAMNSLSENQSLITMPPWCNLWLIGSMALSFTLHFVILYVDVLST
O17314       863 ---------PHLNYYQLSHHLQCLGD---------------PE-NFEGLDCNIFSH---PAPMTMALSVLVTIEMLNALNSLSENQSLLIMPPWVNFWLLAAMALSMTLHFIILYIDILST
Q9XTG6       864 ---------PQITYYQLTHWMRCEIE---------------PD-NFADLDCAVFED---NHPNAMALSVLVTIEMLNAINSLSENQSLLVMPPWKNIWLMAAISLSMSLHFVILYVDIMAT
O96527       872 ---------PQLNYYQLTHHMQCLAE---------------KD-NFHGIDCHIFEN---PKPMTMALSVLVLIEMFNALNSLSENQSLVAMPPWVNIWLVLAMIVSMSLHFLILEVEFLSK
O60900       863 ---------PHINFYQLRNFLKCSED---------------NP-LFAGIDCEVFES---RFPTTMALSVLVTIEMCNALNSVSENQSLLRMPPWMNPWLLVAVAMSMALHFLILLVPPLPL
Q64517       863 ---------PQVTFYQLRNFLKCSED---------------NP-LFAGIDCKVFES---RFPTTMALSVLVTIEMCNALNSVSENQSLLRMPPWLNPWLLGAVVMSMALHFLILLVPPLPL
Q9YGL9       863 ---------PQVSFHQLRNFMRCTED---------------NP-IFEGVNCEIFES---RYPTTMALSVLVTIEMCNALNSVSENQSLLRMPPWLNIWLLGAIVMSMALHFFILYVKPMPL
ATC2_MOUSE   862 ---------PRVSFYQLSHFLQCKED---------------NP-DFDGVDCAIFES---PYPMTMALSVLVTIEMCNALNSLSENQSLLRMPPWENIWLVGSICLSMSLHFLILYVEPLPL
ATC2_RABIT   862 ---------PRVSFYQLSHFLQCKED---------------NP-DFEGVDCAIFES---PYPMTMALSVLVTIEMCNALNSLSENQSLLRMPPWENIWLVGSICLSMSLHFLILYVEPLPL
ATC1_CHICK   863 ---------PSLTYHQLTHFMQCTHH---------------NA-EFEGVDCDIFES---PVPMTMALSVLVTIEMCNALNSLSENQSLLRMPPWVNIWLVGSICLSMSLHFVILYVDPLPM
ATC1_HUMAN   863 ---------PHVNYSQLTHFMQCTED---------------NT-HFEGIDCEVFEA---PEPMTMALSVLVTIEMCNALNSLSENQSLLRMPPWVNIWLLGSICLSMSLHFLILYVDPLPM
ATC1_RANES   863 ---------PNVTFYQLSHFMQCTED---------------NP-DFEGHECEIFES---PVPMTMALSVLVTIEMCNALNSLSENQSLIRMPPWSNFWLLGSICLSMSLHFLILYVEPLPM
ATC1_MAKNI   860 ---------PAVTYYQLSHFMQCHNH---------------NE-DFTGVDCDIFEA---SPPMTMALSVLVTIEMCNALNSLSENQSLIRMPPWSNLWLMAAMTLSMSLHFMIIYVDPLPM
Q27779       865 ---------PKVNYYQLTHHLQCQLE---------------PS-AFKGVNCSVFAS---PKPMTMALSVLVLIEMFNALNSLSENQSLVVMPPWHNMWLIAAICFSMTLHFAILYINVLAN
Q9SWS8       852 ---------PKLTYSELMNFETCALR---------------ET----TYPCSIFED---RHPSTVAMTVLVVVEMFNALNNLSENQSLLVITPRSNLWLVGSIILTMLLHVLILYVHPLAV
ATC1_DUNBI   878 ---------GNMTWSQLTHFQACASQ---------------PGG---AKDCEVFHS---KHPTTISMSVLVVVEMFNALNNLSEDSSLLRIPPWDNKWLVGAIATSMALHFGILYTG-ASA
Q9UUY0       852 ---------PQISFYQLSHFHRCSTE---------------FP----EIGCAMFSNDMAKAGSTVSLSILVVIEMFNAMNALSSSESLLTLPVWKNMMLVYAIGLSMALHFALLYTPILQT
AAF73985     848 IDLTGDGHTLVTYSQLSNWGQCSSW-TTSRPRLSPPEP--ERSRSTTDPCDYFHAGK-VKATTLSLSVLVAIEMFNSLNAS-PDSCLLAMPPWVNPWLLVAMSVSFGLHFLILYVPLLAT
BAA90510     889 IDLTGDGHTLVSYSQLSNWGQCSTW-NNFTVTPFTAGA--RTFTFDDNPCEYFHGGK-VKATTLSLSVLVAIEMFNSLNALSEDTSLLRMPPWVNPWLLLAMSVSFGLHFLILYVPFLAQ
O04987       893 IDLSQDGHSLVSYSQLAHWGQCSSW-EGFKVSPFTAGS--QTFSFDSNPCDYFQQGK-IKASTLSLSVLVAIEMFNSLNALSEDGSLVTMPPWVNPWLLLAMAVSFGLHFVILYVPFLAQ
O23087       889 ISLISDGHTLVSFTQLQNWSECSSWGTNFTATPYTVAGGLRTIAFENNPCDYFTLGK-VKPMTLSLTVLVAIEMFNSLNALSEDNSLLTMPPWRNPWLLVAMTVSFALHCVILYVPFLAN
Q42883       890 INIVSDGHTLVELSQLRNWGECSTW-TNFTVSPFKAGN--RLITFS-DPCEYFTVGK-VKAMTLSLSVLVAIEMFNSLNALSEDNSLIKMPPWRNPWLLVAMSLSFALHSVILYVPFLAD
consensus    961          ' '''''L'''''C'                 ' '''C ''        ''''''''LV''EM N''N''''''L' '''' N''L'''' ''''LH''''''  '
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Figure 2 contd.

```
O96608      943  LFNIAPLGVDPLIVKEAQPFSVLVPSNFDDWKAVIVFSVPVIFIDELLKYITRHMQAS-------RNKKNN-------------------------------------------------
ATC_TRYBB   948  LFNIVPLGVDPHVVQQAQPWSILTPTNFDDWKAVIVFSVPVIFLDELLKFITRRMEKA-------QEKKKD-------------------------------------------------
O09489      956  LFGVTPLGVDADVVATANSWDVLLPTDFTDWKTVLVLSIPVIFLDELLKLFSRCSNHH-------RENHSAEPVVRGLSRIWN-------------------------------------
O77070      955  IFQITPLGFE-------------------EWFAVLKISFPVILIDETLKFFCARKFTDA-------------------------------------------------------------
O96039      955  IFQITPLGFE-------------------EWFAVLKISMPVILIDETLK-FCARKFTDA-------------------------------------------------------------
O96696      956  VFQVTPLSID-------------------EWVTVMKFSIPVVLLDEVLK-FVARKISDAQ-----PTWKL--------------------------------------------------
ATC1_DROME  956  VFQVTPLSAE-------------------EWITVMKFSIPVVLLDETLK-FVARKIADGES----PIYKMHGIVLMWAVFFGLLYAMML-------------------------------
O17314      956  VFQVMPLSVA-------------------QWVAVLKISFPVLLLDETLK-FIARNYTDGEN----NLYKCHWIVLAWATYFAYIKIYFF-------------------------------
Q9XTG6      957  IFQITPLNWV-------------------EWIAVLKISLPVLLLDEILK-FIARNYIDGKPETVGAKARSAISLLAWVSVTLAYFAWMLGPYAELINHALVGPSVDPSKFDAVVTPDKLH
O96527      965  VFQITPLSLE-------------------EWFMVIKISAPVIFIDEILK-LIARRFTDVPS----TVGELK-------------------------------------------------
O60900      956  IFQVTPLSGR-------------------QWVVVLQISLPVILLDEALK-YLSRNHMHACLYPGLLRTVSQAWS-RQPLTTSWTPDHTGLASLKK-------------------------
Q64517      956  IFQVTPLSGR-------------------QWGVVLQMSLPVILLDEALK-YLSRNHMD------GVLGTFMQARS-RQLPTTSRTPYHTGKKGPEVNPGSRGESPVWPSD-----------
Q9YGL9      956  IFQVTPLSWP-------------------QWVVVLKISLPVILLDEGLK-YLSRNHLE------GILRTVRNTWSGEHQLKTCRTPEQ-GRRGQEMNDTKEMLQAKGPQTCNSD-------
ATC2_MOUSE  955  IFQITPLNLT-------------------QWLMVLKISLPVILMDETLK-FVARNYLEQPGKECVQPATKSSCSLSACTDGISWPFVLLIMPLVVWVYSTDTNFSDMFWS----------
ATC2_RABIT  955  IFQITPLNVT-------------------QWLMVLKISLPVILMDETLK-FVARNYLE-PGKECVQPAPQS-CSLWACTEGVSWPFVLLIVPLVMWVYSTDTNFSDLLWS----------
ATC1_CHICK  956  IFKLTHLDLA-------------------HWLVVLRISFPVILLDEALK-FVARNYLEA-------------------------------------------------------------
ATC1_HUMAN  956  IFKLRALDLT-------------------QWLMVLKISLPVIGLDEILK-FVARNYLEDPEDERRK------------------------------------------------------
ATC1_RANES  956  IFKLTPLNVE-------------------QWFIVLKMSFPVILLDELLK-FVARNYLEG-------------------------------------------------------------
ATC1_MAKNI  953  IFKLTHLTFD-------------------QWLMVFKLSFPVILIDEVLK-FFARNYIETGKEVK--------------------------------------------------------
Q27779      958  IFQIAALNIA-------------------EWFAVLKISIPVLLLDETQK-AIVRSSQRG----HSPLYHMAIPMVMWCVYSAFLAFNPL-------------------------------
Q9SWS8      942  LCAVTPLSWA-------------------EWTAVLYLSFPVIIIDELLKFLSR--------NTGMRFRFRLRKADLLPKDRRDK------------------------------------
ATC1_DUNBI  968  MFGVTGLSFA-------------------EWTMVIKLSAPVILVDEIMKAWSRRRQRHPASSRGGPVSLMEIQVPLTSSSRDEAALKLK-------------------------------
Q9UUY0      945  LFSILPMNWA-------------------EWKAVIVISAPVVLLDELLKAVER------------KYFVQSTPSSTSSDKKKDL------------------------------------
AAF73985    963  VFGIVPLSLNEWLS-----------------LVLLMVALPVVLIDEALKLAGRCTSP------ASGPTRRSRKKKQKASSERRLTFDLRAQLLNHSINHVNKR-----------------
BAA90510   1005  VFGIVPLSLNEWL-------------------LVLLVALPVVLIDEVLKFVGRCTS-------SSGPKRRTRK--QK--GE---------------------------------------
O04987     1009  VFGIVPLSLNEWL-------------------LVLAVSLPVILIDEVLKFVGRCTSGY-----RYSPRTLSTK--QK--EE---------------------------------------
O23087     1008  VFGIVPLSFREWF-------------------VVILVSFPVILIDEALKFIG-RCRRT-----RIKKKIKTM------------------------------------------------
Q42883     1005  IFGIVPLSLYEWL-------------------LVILLSAPVILIDEVLKFVGRRRRRT-----KLKAA----------------------------------------------------
consensus  1081  ''''''''''                      ' ''''''PV'''DE''K '' '    '
```

Figure 2 contd.

O96608		---
ATC_TRYBB		---
O09489		---
O77070		---
O96039		---
O96696		---
ATC1_DROME		---
O17314		---
Q9XTG6	1057	NEL
O96527		---
O60900		---
Q64517		---
Q9YGL9		---
ATC2_MOUSE		---
ATC2_RABIT		---
ATC1_CHICK		---
ATC1_HUMAN		---
ATC1_RANES		---
ATC1_MAKNI		---
Q27779		---
Q9SWS8		---
ATC1_DUNBI		---
Q9UUY0		---
AAF73985		---
BAA90510		---
O04987		---
O23087		---
Q42883		---
consensus	1201	

Figure 3: Sequence of pcDNA3 containing *Arabidopsis* SERCA cDNA

gatccatggaagacgcctacgccagatctgtctcagaggtgcttgatttctttggggtagacccaacaaagggtctt
tctgattctcaggttgttcatcattccaggctttatggcaggaatgtactgcctgaagagaaaagaacgccattctg
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gcagtgggggtgatcacggagactaatgctgagaaggctcttgaggagctacgtgcctaccaagcaaatatagctac
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accgtgccccacggtcaacaaactatttcctatgataatgagaacgacctgacgtttattgggttggtgggaatgct
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cacttgccagcgccctagcgcccgctcctttcgctttcttcccttcctttctcgccacgttcgccggctttccccgt
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ggcacaacagacaatcggctgctctgatgccgccgtgttccggctgtcagcgcaggggcgcccggttctttttgtca

Fig 3 contd

agaccgacctgtccggtgccctgaatgaactgcaggacgaggcagcgcggctatcgtggctggccacgacgggcgtt
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Figure 4: Sequence of pcDNA3 containing *Heliothis* SERCA cDNA

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Fig 4 contd

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Figure 5: Heliothis SERCA cDNA cloned into pDW2600 (*sca-1* promoter)

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Fig 5 contd

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Fig 5 contd

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Figure 6: Arabidopsis SERCA cDNAcloned into pDW2600 (*sca-1* promoter)

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Fig 6 contd

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Fig 6 contd

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Figure 7: pDW2700 (general cloning vector containing *myo-2* promo___,

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Fig 7 contd

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cgactctagag

Figure 8: pDW2800 (general cloning vector containing *myo-3* promoter)

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Fig 8 contd

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Figure 9: pDW2400 (general cloning vector containing *egl-15* promoter)

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Fig 9 contd

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Figure 10: pDW2422 (general cloning vector containing *ceh-24* promoter)

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Fig 10 contd

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Figure 11: pDW2721 (GFP cloned into pDW2700).

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Fig 11 contd

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aaggacccaaaggtatgtttcgaatgatactaacataacatagaacattttcaggaggacccttggctagcgtcgacg
gtaccatgggg

FIG. 12.

GAACGAAATGCTGAATCGGCCATCGAAGCGCTCAAGGAATACGAACCAGAAATGGCCA
AGGTCATCCGATCCGGACACCACGGAATTCAGATGGTTCGCGCTAAGGAACTCGTGCC
AGGAGATCTTGTCGAAGTTTCAGgttagcaaaaactttttttttaactttcaaattt
taaaccatatattttcagTCGGAGACAAGATCCCAGCCGATCTCCGTCTTGTGAAGA
TCTACTCCACCACCATCCGTATCGATCAGTCCATCCTCACCGGAGAATCTGTGTCTGT
TATCAAGCACACCGACTCTGTGCCAGATCCACGCGCTGTTAACCAGGACAAGAAGAAT
TGTCTGTTCTCGGGAACCAATGTCGCATCTGGAAAGGCTCGTGGAATCGTCTTCGGAA
CCGGATTGACCACTGAAATCGGAAAGATCCGTACCGAAATGGCTGAGACCGAGAATGA
GAAGACACCACTTCAACAGAAGTTGGACGAATTCGGAGAGCAACTTTCCAAGGTTATC
TCTGTTATTTGCGTTGCTGTTTGGGCTATCAACATTGGACATTTCAACGATCCAGCTC
ACGGTGGATCATGGGTTAAGGGAGCAATCTACTACTTCAAAATCGCCGTTGCTCTTGC
CGTCGCTGCTATTCCAGAAGGACTTCCAGCTGTCATCACCACGTGCCTTGCCCTCGGA
ACTCGCCGTATGGCCAAGAAGAACGCTATTGTAAGATCCCTTCCATCCGTCGAAACTC
TTGGATGCACATCTGTTATCTGCTCTGACAAGACTGGAACTCTCACCACCAACCAGAT
GTCTGTGTCAAAGATGTTCATCGCTGGACAAGCTTCTGGAGACAACATCAACTTCACC
GAGTTCGCCATCTCCGGATCCACCTACGAGCCAGTCGGAAAGGTTTCCACCAATGGAC
GTGAAATCAACCCAGCTGCTGGAGAATTCGAATCACTCACCGAGTTGGCCATGATCTG
CGCTATGTGCAATGATTCATCTGTTGATTACAATGAGACCAAGAAGATCTACGAGAAA
GTCGGAGAAGCCACTGAAACTGCTCTTATCGTTCTTGCTGAGAAGATGAATGTTTTCG
GAACCTCGAAAGCCGGACTTTCACCAAAGGAGCTCGGAGGAGTTTGCAACCGTGTCAT
CCAACAAAAATGGAAGAAGGAGTTCACACTCGAGTTCTCCCGTGATCGTAAATCCATG
TCCGCCTACTGCTTCCCAGCTTCCGGAGGATCTGGAGCCAAGATGTTCGTGAAGGGAG
CCCCAGAAGGAGTTCTCGGAAGATGCACCCACGTCAGAGTTAACGGACAAAAGGTTCC
ACTCACCTCTGCCATGACTCAGAAGATTGTTGACCAATGCGTGCAATACGGAACCGGA
AGAGATACCCTTCGTTGTCTTGCCCTCGGAACCATCGATACCCCAGTCAGCGTTAGCA
ACATGAACCTCGAAGACTCTACCCAATTCGTCAAATACGAACAAGACATCACATTTGT
CGGAGTCGTCGGAATGCTTGACCCCCCAAGAACTGAAGTTTCGGACTCGATCAAGGCT
TGTAACCACGCTGGAATCCGTGTCATCATGATCACCGGAGACAACAAGAACACCGCTG
AGGCTATCGGAAGAAGAATCGGACTCTTCGGAGAGAACGAGGATACCACTGGAAAAGC
TTACACTGGACGTGAATTTGACGATCTTCCACCAGAGCAACAATCTGAAGCCTGCCGC
AGAGCTAAGCTTTTCGCCCGTGTCGAGCCATCTCACAAGTCCAAGATTGTCGATATCC
TTCAATCCCAGGGAGAGATTACTGCTATGACCGGAGACGGAGTCAACGACGCTCCAGC
TTTGAAGAAGGCCGAAATCGGAATTTCTATGGGATCAGGAACTGCTGTCGCCAAGTCT
GCATCTGAAATGGTTCTTGCTGACGATAACTTCGCATCCATTGTGTCTGCTGTCGAAG
AAGGACGTGCTATTTACAACAACATGAAACAATTCATCAGATATCTCATCTCATCTAA
CGTCGGAGAAGTCGTCTCCATCTTCATGGTCGCCGCACTCGGAATTCCAGAGGCTCTC
ATTCCAGTTCAACTTCTCTGGGTTAACTTGGTCACTGACGGTCTTCCAGCCACTGCTC
TCGGATTCAATCCACCAGATCTTGACATTATGGACAGACATCCACGTTCAGCCAACGA
TGGACTCATCTCTGGATGGCTCTTCTTCAGATATCTTGCTGTCGGAA

FIG. 13.

gaattcgaatcactcaccgagttggccatgatctgcgctatgtgcaatgattcatctgttgattacaatgagaccaagaagatc
tacgagaaagtcggagaagccactgaaactgctcttatcgttcttgctgagaagatgaatgttttcggaacctcgaaagccg
gactttcaccaaaggagctcggaggagtttgcaaccgtgtcatccaacaaaaatggaagaaggagttcacactcgagttct
cccgtgatcgtaaatccatgtccgcctactgcttcccagcttccggaggatctggagccaagatgttcgtgaagggagccc
cagaaggagttctcggaagatgcacccacgtcagagttaacggacaaaggttccactcacctctgccatgactcagaag
attgttgaccaatgcgtgcaatacggaaccggaagagatacccttcgttgtcttgccctcggaaccatcgataccccagtca
gcgttagcaacatgaacctcgaagactctacccaattcgtcaaatacgaacaagacatcacatttgtcggagtcgtcggaat
gcttgacccccccaagaactgaagtttcggactcgatcaaggcttgtaaccacgctggaatccgtgtcatcatgatcaccgga
gacaacaagaacaccgctgaggctatcggaagaagaatcggactcttcggagagaacgaggataccactggaaagctt

FIG. 14.

ctagttttgaaatccaaaaaaaaaacaaagttcaataaaatgttacccaattgtgcgatttttgctttaaaaatacggtacccggt
ctcgatgcggcaattgtttggtaaatgtaaaagggtgtgcgcctttaaagagtactgtaatttcaatcttccgacactgctgaat
ttttattgactttttgttcattaatttatatatgatttattggtatgttaaaaaaacacccatttcaaatctattaaaattccacaacaa
caaaagttcgagattacagtactttttagaggcgcacatcctttttgggatactaaacaattgtcgcgtcgagaccaggtacca
tatttccaaaacacaatttcgcgtgtaaataaaaaatatcaacataataatttccatttttcgaaatttaaagttaatcactttttggtt
tagattatgatttcacacgttttttccttctagttctcttttttttgttatttgcctgaaaaatggtctgaaaacttaggcaatcagcaa
tgtgtcacataatttctcccagagaaatccctttcaacaaaatctcccggattgacctgtgtgctcgaccttgataaattggttgg
cagctctctggcttatcttttgagaggaaaaagatccaacaaatttttatctcccttatcccttttctcttcatcactaccaataata
atagtttttttttcgtcgcggaagcaaaatggcgaacaagtgttggaataagagtactccagggatttaagggctgaaagcc
agtgatttatgagctccaatttttcagatgtttttcctccatcgcgtatttgtctaaacattcgatttcttcctgcttcccaacttttc
aaatcgaaataaaagagcatctgtcgctttttatcgatgtgcttctgtgagactaaagaactactcgttttcactcgttctctctct
ctcaactatcaaagttttgttgattgcgtgtgtcagcttccttctttttattatcatcttttcattggaggaaaaaaataacttctgaag
agcaaaagaactaacttcggggaatacagagaaaattcctgtaaaaatctggaaattttttcgcttaactcgaaatatttagtttt
tcactgtgatttctgggaaaaatcaagaaatatttgcctaaaacacgagttttcacatgaaaaatgaattatttattgatttttttatg
gagattacaaaaaagacacacgtgaaactactgctaccgtagttgtgtaaacgtagtgttctctatttagacctgtttaatgtat
ttttttgcagttgaaaattttaaaaatatttagttatttttaaaaatatttaatttacaaaataattagcctgaacccatgaaaagata
cgttatatttaatttttaccgtaagactttcaagatcgttgcgagacccggcgcctaggtcaaagagcctccctttaaacccatc

FIG. 14 (CONTD 1).

aacacgttttgcctttttcatcgatttttgcagttcttttcttctttccaactgatttttcttcattttaaagttttttcctcatttttcccat
ttgaaattatttaaacacgtgcaaccagctggtaacatgtgtcacatgccgttatctaacttcaaaacagtacatttccgatcac
acgtcccccgcgccgagtttatagtttcattaataactttttcggtttttgataatactaattgagtttattaattgtttccatattcat
ctagcactttgacctgtccttcttcgaattctcaaatatttgcactctgggtttaggtgtgaaaagaattgtcgtcattaagcggg
gcatccggggcaccgaaaaaagccctccgatttaacgaatttgagataaagttggagagagagcccagtgtttgcttgcc
caagatatatatcttggatttatcaattactgtttgtcaacctgtcgccggcgcccccttttgctcttgctcccacgccccgaga
ttgaatttcaattttatttcgaagtaagtctcttgattgtttcgaaaatccgatgacagttttcattactttttgtctgttgattttgtag
ggaaacattgaaatttttctgatctttctttgatcttatgatttttcatttattccaattaaaaaaaattagcgcattcagaaccagagt
gaagcttgagatgttgtaggtttatcaaaagatcaaaatctcgaattccttcgaaatgtttttagttttcgacttccgtgtgatttct
agcgatcctgacagagatcactgaattttaatgttatcgagattgttgtgtaggctccatctcctctctgaagcttctgattttgcc
gaaagtctagttacttgccgactgctgacactaggatatcccactaccgtacccattgttggatccgtactctgctgcgacttct
tctctgtttcacgtgaacctccgggatcgtcggtaagccccgcccgttatctgtgccaacttgtcttcgtgccctcgagcgac
gagctcattcaatcacgccacgacctccgtctggacagatgctctcattgtctctgcgtctccaagtattcgtcacactatctca
tgcattctattcaaaacgcgagagaaagcgcgggaacgagagagagttcagacagatcgaacttgtttttatcccccccc
cctcgtccggctgcagagcaaaaaaatactgcttttccttgcaaaattcggtgctttcttcaaagagaaacttttgaagtcggc
gcgagcatttccttctttgacttctctctttccgccaaaaagcctagcatttttattgataatttgattacacacactcagagttcttc
gacatgataaagtgtttcattggcactcgccctaacagtacatgacaagggcggattattatcgatcgatattgaagacaaac
tccaaatgtgtgctcattttggagccccgtgtggggcagctgctctcaatatattactagggagacgaggagggggacctta
tcgaacgtcgcatgagccattctttcttctttatgcactctcttcactctctcacacattaatcgattcatagactcccatattccttg
atgaaggtgtgggtttttagctttttttcccgatttgtaaaaggaagaggctgacgatgttaggaaaaagagaacggagccga
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aaaaattagtttcaatttttttaattactaaataggcaaaagtttttcaagaactctagaaaaactagcttaattcatgggtacta
gaaaaattcttgttttaaatttaatatttatcttaagatgtaattacgagaagctttttgaaaattctcaattaaaagaatttgccgat
ttagaataaaagtcttcagaaatgagtaaaagctcaaattagaagtttgtttttaaaggaaaaacacgaaaaaagaacactatt
tatcttttcctccccgcgtaaaattagttgttgtgataatagtgatccgctgtctatttgcactcggctcttcacaccgtgcttcctc
tcacttgacccaacaggaaaaaaaaacatcacgtctgagacggtgaattgccttatcaagagcgtcgtctctttcacccagta
acaaaaaaaaatttggtttctttactttatatttatgtaggtcacaaaaaaaaagtgatgcagttttgtgggtcggttgtctccacac
cacctccgcctccagcagcacacaatcatcttcgtgtgttctcgacgattccttgtatgccgcggtcgtgaatgcaccacattc
gacgcgcaactacacaccacactcactttcggtggtattactacacgtcatcgttgttcgtagtctcccgctctttcgtccccac
tcactcctcattattccccttggtgtattgatttttttaaatggtacaccactcctgacgtttctaccttcttgttttccgtccatttag
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ctcgcttgtttctcaaaatatgagatcaacggatttttttccttctcgattcaatttttgctgcgctctgtctgccaaagtgtgtgtgt
ccgagcaaaagatgagagaatttacaaacagaaatgaaaaaaagttggccaaataatgaagttttatccgagattgatggg

FIG. 14 (CONT'D 2).

aaagatattaatgttctttacggtttggaggggagagagagatagattttcgcatcaaactccgccttttacatgtcttttagaat
ctaaaatagatttttctcatcattttaatagaaaatcgagaaattacagtaatttcgcaattttcttgccaaaaatacacgaaattt
gtgggtctcgccacgatctcggtcttagtggttcatttggtttaaaagtttataaaatttcaaattctagtgtttaatttccgcataat
tggacctaaaatgggtttttgtcatcattttcaacaagaaatcgtgaaaatcctgttgtttcgcaattttcttttcaaaaatacacga
aatatatggtaatttcccgaaatattgagggtctcgccacgatttcagtcacagtggccaggatttatcacgaaaaaagttcgc
ctagtctcacatttccggaaaaccgaatctaaattagtttttgtcatcattttgaacaaaaaatcgagacatccctatagtttcgc
aattttcgtcgcttttctctccaaaaatgacagtctagaattaaaattcgctggaactgggaccatgatatcttttctccccgttttt
cattttatttttattacactggattgactaaaggtcaccaccaccgccagtgtgtgccatatcacacacacacacacacacaat
gtcgagattttatgtgttatccctgcttgatttcgttccgttgtctctctctctattcatcttttgagccgagaagctccagagaat
ggagcacacaggatcccggcgcgcgatgtcgtcgggagatggcgccgcctgggaagccgccgagagatatcagggaa
gatcgtctgatttctcctcggatgccacctcatctctcgagtttctccgcctgttactccctgccgaacctgatatttcccgttgtc
gtaaagagatgtttttatttacttacaccgggtcctctctctctgccagcacagctcagtgttggctgtgtgctcgggctcctg
ccaccggcggcctcatcttcttcttcttcttctctcctgctctcgcttatcacttcttcattcattcttattccttttcatcatcaaacta
gcatttcttactttatttatttttttcaattttcaattttcagataaaaccaaactacttgggttacagccgtcaacatggaggacgcg
catgccaaagacgccaatgaggtactttttatagtttttaaattttagtttttaatacaatttatttttccaggtgtgcaaattcttcgga
acgggtccggagggattgactccacagcaagttgaaacattgaggaacaaatatggagaaaatggttggtttttacatgga
tttctcattaaaaattgaatttttccagaaatgcccgccgaagagggaaaatcactgtgggagctgattctcgagcaattcga
cgatcttctcgtcaagattctcctcctcgccgccatcatctcgtttgtgctcgcccttttcgaagagcacgaagatcagacaga
agcagtgacggcgttcgtcgaaccgttcgtcatccttctcattcttattgccaacgcgaccgtcggagtgtggcaggtagga
acaacacagacaggcgcacgcgctgaaagaaaataagaagaagaagaaaaagcacagttgttttctgtgtttttgtagatc
aaaagaaaggaactaggagtgattgcacagagagagagagagagaaataatgtcttttgacttgtttttgttggtgagaga
gatagggaaaaagagtccctaaagaaaaaatagtgtaacgggcggtccggaagaaatgctctttgcgccgaaaagtttttg
aaaaaagaagaaaatgatgaaggaaaggcgtgcgtcatgagcttcgcatttacgtacgcaaaaagtgagggatatgtgaa
aaagatattgggtgatagaatagttgatggattgggctgcactatttgcctcaatttgccacaaatttccatctaatttgtcataat
tttccaggaacgaaatgctgaatcggccatcgaagcgctcaaggaatacgaaccagaaatggccaaggtcatccgatccg
gacaccacggaattcagatggttcgcgctaaggaactcgtgccaggagatcttgtcgaagtttcaggttagcaaaaactttttt
tttttaactttcaaattttaaaccatatatttttcagtcggagacaagatcccagccgatctccgtcttgtgaagatctactccacc
accatccgtatcgatcagtccatcctcaccggagaatctgtgtctgttatcaagcacaccgactctgtgccagatccacgcgc
tgttaaccaggacaagaagaattgtctgttctcgggaaccaatgtcgcatctggaaaggctcgtggaatcgtcttcggaacc
ggattgaccactgaaatcggaaagatccgtaccgaaatggctgagaccgagaatgagaagacaccacttcaacagaagtt
ggacgaattcggagagcaactttccaaggttatctctgttatttgcgttgctgtttgggctatcaacattggacatttcaacgatc
cagctcacggtggatcatgggttaagggagcaatctactacttcaaaatcgccgttgctcttgccgtcgctgctattccagaa
ggacttccagctgtcatcaccacgtgccttgccctcggaactcgccgtatggccaagaagaacgctattgtaagatcccttc
catccgtcgaaactcttggatgtacatctgttattctgctctgacaagactggaactttcaccaccaactcagatgtctgtgtcaa

FIG. 14 (CONTD 3).

agatgttcatcgctggacaagcttctggagacaacatcaacttcaccgagttcgccatctccggatccacctacgagccagt
cggaaaggtttccaccaatggacgtgaaatcaacccagctgctggagaattcgaatcactcaccgagttggccatgatctg
cgctatgtgcaatgattcatctgttgattacaatgagaccaagaagatctacgagaaagtcggagaagccactgaaactgct
cttatcgttcttgctgagaagatgaatgttttcggaacctcgaaagccggactttcaccaaaggagctcggaggagtttgcaa
ccgtgtcatccaacaaaaatggaagaaggagttcacactcgagttctcccgtgatcgtaaatccatgtccgcctactgcttcc
cagcttccggaggatctggagccaagatgttcgtgaagggagccccagaaggagttctcggaagatgcacccacgtcag
agttaacggacaaaaggttccactcacctctgccatgactcagaagattgttgaccaatgcgtgcaatacggaaccggaag
agataccccttcgttgtcttgccctcggaaccatcgataccccagtcagcgttagcaacatgaacctcgaagactctacccaat
tcgtcaaatacgaacaagacatcacatttgtcggagtcgtcggaatgcttgacccccccaagaactgaagtttcggactcgat
caaggcttgtaaccacgctggaatccgtgtcatcatgatcaccggagacaacaagaacaccgctgaggctatcggaagaa
gaatcggactcttcggagagaacgaggataccactggaaaagcttacactggacgtgaatttgacgatcttccaccagagc
aacaatctgaagcctgccgcagagctaagcttttcgcccgtgtcgagccatctcacaagtccaagattgtcgatatccttcaa
tcccagggagagattactgctatgaccggagacggagtcaacgacgctccagctttgaagaaggccgaaatcggaatttct
atgggatcaggaactgctgtcgccaagtctgcatctgaaatggttcttgctgacgataacttcgcatccattgtgtctgctgtc
gaagaaggacgtgctatttacaacaacatgaaacaattcatcagatatctcatctcatctaacgtcggagaagtcgtctccatc
ttcatggtcgccgcactcggaattccagaggctctcattccagttcaacttctctgggttaacttggtcactgacggtcttccag
ccactgctctcggattcaatccaccagatcttgacattatggacagacatccacgttcagccaacgatggactcatctctgga
tggctcttcttcagatatcttgctgtcggaagtacgtttaaaaaattcccctaaaaaagtataattctaaaattgaaattttccagc
ctacgtcggagttgccaccgtcggagcctcaatgtggtggttcttgttgtacgaggagggaccacagatcacctactaccag
ctcactcactggatgagatgtgaaatcgagccagacaactttgccgatcttgactgcgccgtattcgaggacaatcacccga
acgccatggctctgtccgtgcttgtcaccattgagatgctcaacgccatcaactcactttccgagaatcaatcgcttttagtgat
gccaccatggaagaacatctggctgatggccgccatttccctttcgatgtctcttcactttgtcattctctacgttgacatcatgg
ccaccatcttccaggtatcacaattaatcatatattaatcgaaacatctaattcaaatcttcagatcacccctctcaactgggtcg
aatggatcgccgtgttgaagatctcactgccagtgctccttctcgatgaaattctcaagttcatcgccagaaactacatcgacg
gtaagccggagacggtcggcgcgaaggcacgtagtgccatctcgctgctcgcctgggtgtctgtgacgctcgcctactttg
cgtggatgttgggcccgtacgccgagctcattaaccatgcgctcgtcggtccatctgtcgatccgtcgaaattcgacgcggt
tgtcacgcccgacaagttacataacgaattgtgattgaagttcttctaacccccaaaccaaccgcctctcaaacaacttgtgat
gatttctctttatttctctctctttcttgttctaatcattttgggcctttttccctttttctctctgcagtgtgttaactgatccataatcctt
cgtgtaaacccccctctccctactttaggatttcttcctcgttgctcattgtatttgtccaaatcgccacaatttccctacaaatat
atatgttttttttgctaatttttgtgtttcccttccttcttgtccactgaaagttctacgtctctcgctctccacatccccattgttctcc
cctttttcataataatttattattatcctttttttaaattaattttgttgcgtgtgaatctattaggagctcacaaataaaagtgatcctt
taaaaaaccttacttccttctgtttttctctaacctaaccaatgtgtctgttcagggagtgcctcttttctttaccgaatggtgtgca
attttgtcgactgtcgatctcgtccatggcaatgcaggatttgaaactaaatttccctggaaaaagaaataattttggtgattttca
[illegible]

FIG. 14 (CONTD 4).

catttttcagactctttcatatttctaagttttccaatttttttcttttgtagtgcgatcgttttcgtttcgagacccgaaatcgaaag
gatctcttttagagatctttaggatctttttctttgctcaactcatcattctttgtttttcttctatatcctcttgttgacggtgatcaga
caaatttgttagaaatattattacatttcctttaggtttcttctattaaaaaaaaagaaaacttctgctaaattcgtgtacgttgtctct
cccatttctcattaaaaatcgatattaattgtaattttggtttgtcctccagtgtcgtgtgcgccatcgatggaaataaaaaagttt
caaaactattatagcttttcttttatgaaaaatataaaatacaattagaatgtttttgttaaatgcgatacggtgtgcgcctttaaag
agtagagtactgtagttccaaaattttgttggtgcgggattttcattgatttttcatcgtttttcgacaaaaatatatttatttattgaa
aaaagttaaataaaactattaaaaacacagaatttttaacaaattgtgaaaaacacatgaaaaatcgatgacaattctacagta
acgaacattttgaattacagtaatctttaaaggcgcgcacacgtttgcatttaattaaaatgtgtcgtgtcgagaccgactacca
cgtctcgttattatagaacgagcaattacagcctaacatcaactcagaacaaaccaggatcccacgcaagtttaaaggagca
tgctgggtatcacaacgatttttgaagagaacgaggccccacgaaacggggagcagaacgaaaaggggatctgcaaaa
aggggatctgcaaaaaggggatctgcgaaaaggggagatatgaaaaggggagatacgaaaaggggagctggcactgt
gccaaacgcacaaaacgcaatttttctcacgcaacgcacgttgatttttgaaattttcttctagaagatacgcttaacaacacgc
gacgcgg

FIG. 15.

ttggttggcagctctctggcttatcttttgagaggaaaaagatccaacaaatttttatctcccttatcccttttctcttcatcactac
caataataatagttttttttcgtcgcggaagcaaaatggcgaacaagtgttggaataagagtactccagggatttaagggct
gaaagccagtgatttatgagctccaatttttcagatgtttttcctccatcgcgtatttgtctaaacattcgattttcttcctgcttccc
aactttcaaatcgaaataaaagagcatctgtcgctttttatcgatgtgcttctgtgagactaaagaactactcgttttcactcgtt
ctctctctcaactatcaaagttttgttgattgcgtgtgtcagcttccttctttttattatcatcttttcattggaggaaaaaaataact
tctgaagagcaaaagaactaacttcggggaatacagagaaaattcctgtaaaaatctggaaatttttcgcttaactcgaaata
tttagtttttcactgtgatttctgggaaaaatcaagaaatatttgcctaaaacacgagttttcacatgaaaaatgaattatttattgat
tttttatggagattacaaaaaagacacacgtgaaactactgctaccgtagttgtgtaaacgtagtgttctctatttagacctgttt
aatgtattttttgcagttgaaaatttttaaaaatatttagttatttttaaaaatatttaatttacaaaataattagcctgaacccatga
aaagatacgttatatttaatttttaccgtaagactttcaagatcgttgcgagacccggcgcctaggtcaaagagcctccctttaa
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gatcacacgtcccccgcgccgagttttatagtttcattaataactttcggtttttgataatactaattgagttttattaattgtttcca
tattcatctagcactttgacctgtccttcttcgaattctcaaatatttgcactctgggtttaggtgtgaaaagaattgtcgtcattaa
gcggggcatccggggcaccgaaaaaagccctccgatttaacgaatttgagataaagttggagagagagcccagtgtttg
cttgcccaagatatatatcttggatttatcaattactgtttgtcaacctgtcgccggcgcccccttttgctcttgctcccacgccc
cgagattgaatttcaatttatttcgaagtaagtctcttgattgtttcgaaaatccgatgacagtttcattactttttgtctgttgattt

FIG. 15 (CONT'D 1).

tgtagggaaacattgaaattttctgatctttctttgatcttatgatttttcatttattccaattaaaaaaaattagcgcattcagaacc
agagtgaagcttgagatgttgtaggtttatcaaaagatcaaaatctcgaattccttcgaaatgtttttagttttcgacttccgtgtg
atttctagcgatcctgacagagatcactgaattttaatgttatcgagattgttgtgtaggctccatctcctctctgaagcttctgatt
ttgccgaaagtctagttacttgccgactgctgacactaggatatcccactaccgtacccattgttggatccgtactctgctgcg
acttcttctctgtttcacgtgaacctccgggatcgtcggtaagccccgcccgttatctgtgccaacttgtcttcgtgccctcgag
cgacgagctcattcaatcacgccacgacctccgtctggacagatgctctcattgtctctgcgtctccaagtattcgtcacacta
tctcatgcattctattcaaaacgcgagagaaagcgcgggaacgagagagagttcagacagatcgaacttgtttttatccccc
ccccctcgtccggctgcagagcaaaaaaatactgcttttccttgcaaaattcggtgctttcttcaaagagaaactttgaagtc
ggcgcgagcatttccttctttgacttctctctttccgccaaaaagcctagcatttttattgataatttgattacacacactcagagtt
cttcgacatgataaagtgtttcattggcactcgccctaacagtacatgacaagggcggattattatcgatcgatattgaagaca
aactccaaatgtgtgctcattttggagccccgtgtggggcagctgctctcaatatattactagggagacgaggaggggac
cttatcgaacgtcgcatgagccattctttcttctttatgcactctcttcactctctcacacattaatcgattcatagactcccatattc
cttgatgaaggtgtgggtttttagcttttttcccgatttgtaaaaggaagaggctgacgatgttaggaaaaagagaacggagc
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aataaaaattagtttcaatttttttaattactaaataggcaaaagtttttcaagaactctagaaaaactagcttaattcatgggtac
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ctcacttgacccaacaggaaaaaaaaacatcacgtctgagacggtgaattgccttatcaagagcgtcgtctctttcacccagt
aacaaaaaaaatttggtttctttactttatatttatgtaggtcacaaaaaaaaagtgatgcagttttgtgggtcggttgtctccaca
ccacctccgcctccagcagcacacaatcatcttcgtgtgttctcgacgattccttgtatgccgcggtcgtgaatgcaccacatt
cgacgcgcaactacacaccacactcactttcggtggtattactacacgtcatcgttgttcgtagtctcccgctctttcgtcccca
ctcactcctcattattccccttggtgtattgatttttttaaatggtacaccactcctgacgtttctaccttcttgttttccgtccattta
gattttatctggaaatttttttaaaatttaggccagagagttctagttcttgttctaaaagtctaggtcagacatacattttctatttct
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cctcgcttgtttctcaaaatatgagatcaacggatttttccttctcgattcaatttttgctgcgctctgtctgccaaagtgtgtgtg
tccgagcaaaagatgagagaatttacaaacagaaatgaaaaaaagttggccaaataatgaagttttatccgagattgatggg
aaagatattaatgttctttacggtttggaggggagagagagatagattttcgcatcaaactccgccttttacatgtcttttagaat
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gtgggtctcgccacgatctcggtcttagtggttcatttggtttaaaagtttataaaatttcaaattctagtgtttaatttccgcataat
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aatatatggtaatttcccgaaatattgagggtctcgccacgatttcagtcacagtggccaggatttatcacgaaaaaagttcgc
ctagtctcacatttccggaaaaccgaatctaaattagtttttgtcatcatttgaacaaaaaatcgagacatccctatagtttcgc
aatttcatcagtttgtctccaaaaatcacagtctagaattaaaattcgctggaactgggaccatgatatcttttctccccgttttt

FIG. 15 (CONTD 2).

cattttattttttattacactggattgactaaaggtcaccaccaccgccagtgtgtgccatatcacacacacacacacacacaat
gtcgagattttatgtgttatccctgcttgatttcgttccgttgtctctctctctattcatcttttgagccgagaagctccagagaat
ggagcacacaggatcccggcgcgcgatgtcgtcgggagatggcgccgcctgggaagccgccgagagatatcagggaa
gatcgtctgatttctcctcggatgccacctcatctctcgagtttctccgcctgttactccctgccgaacctgatatttcccgttgtc
gtaaagagatgtttttattttacttacaccgggtcctctctctctgccagcacagctcagtgttggctgtgtgctcgggctcctg
ccaccggcggcctcatcttcttcttcttcttctctcctgctctcgcttatcacttcttcattcattcttattcctttcatcatcaaacta
gcatttcttactttatttattttttcaatttcaattttcagataaaaccaaactacttgggttacagccgtcaaca

FIG. 16.

ctgcagagcaaaaaaatactgcttttccttgcaaaattcggtgctttcttcaaagagaaactttgaagtcggcgcgagcatttc
cttctttgacttctctctttccgccaaaaagcctagcatttttattgataatttgattacacacactcagagttcttcgacatgataaa
gtgtttcattggcactcgccctaacagtacatgacaagggcggattattatcgatcgatattgaagacaaactccaaatgtgtg
ctcattttggagccccgtgtggggcagctgctctcaatatattactagggagacgaggaggggggaccttatcgaacgtcgc
atgagccattctttcttctttatgcactctcttcactctctcacacattaatcgattcatagactcccatattccttgatgaaggtgtg
ggtttttagctttttttcccgatttgtaaaaggaagaggctgacgatgttaggaaaaagagaacggagccgaaaaaacatccg
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aattttttttaattactaaataggcaaaagtttttcaagaactctagaaaaactagcttaattcatgggtactagaaaaattcttgtt
ttaaatttaatatttatcttaagatgtaattacgagaagctttttgaaaattctcaattaaaagaatttgccgatttagaataaaagt
cttcagaaatgagtaaaagctcaaattagaagtttgtttttaaaggaaaaacacgaaaaaagaacactatttatcttttcctccc
cgcgtaaaattagttgttgtgataatagtgatccgctgtctatttgcactcggctcttcacaccgtgcttcctctcacttgaccca
acaggaaaaaaaaacatcacgtctgagacggtgaattgccttatcaagagcgtcgtctctttcacccagtaacaaaaaaaatt
tggtttctttactttatatttatgtaggtcacaaaaaaaaagtgatgcagttttgtgggtcggttgtctccacaccacctccgcctc
cagcagcacacaatcatcttcgtgtgttctcgacgattccttgtatgccgcggtcgtgaatgcaccacattcgacgcgcaact
acacaccacactcactttcggtggtattactacacgtcatcgttgttcgtagtctcccgctctttcgtccccactcactcctcatta
ttccccttggtgtattgattttttaaaatggtacaccactcctgacgtttctaccttcttgttttccgtccatttagatttatctggaaa
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gttgataaagaaaactggttattcagaaagagtgtgtctcgttgaaattgattcaaaaaaaaattcccacccctcgcttgtttctc
aaaatatgagatcaacggatttttccttctcgattcaatttttgctgcgctctgtctgccaaagtgtgtgtgtccgagcaaaag
atgagagaatttacaaacagaaatgaaaaaaagttggccaaataatgaagttttatccgagattgatgggaaagatattaatg
ttctttacggtttggaggggagagagagatagatttcgcatcaaactccgccttttacatgtcttttagaatctaaaatagattttt
ctcatcattttaatagaaaatcgagaaattacagtaatttcgcaattttcttgccaaaaatacacgaaatttgtgggtctcgcca
aaatcgaatcggaattagtggaacttggaacttagaaatttcaaatctactattgagttcccatgatcaacgtaaaatg

FIG. 16 (CONTD).

ggtttttgtcatcattttcaacaagaaatcgtgaaaatcctgttgtttcgcaattttcttttcaaaaatacacgaaatatatggtaatt
tcccgaaatattgagggtctcgccacgatttcagtcacagtggccaggatttatcacgaaaaaagttcgcctagtctcacattt
ccggaaaaccgaatctaaattagtttttgtcatcattttgaacaaaaaatcgagacatccctatagtttcgcaattttcgtcgcttt
tctctccaaaaatgacagtctagaattaaaattcgctggaactgggaccatgatatcttttctccccgtttttcattttatttttatta
cactggattgactaaaggtcaccaccaccgccagtgtgtgccatatcacacacacacacacacacaatgtcgagattttatgt
gttatccctgcttgatttcgttccgttgtctctctctctattcatcttttgagccgagaagctccagagaatggagcacacagg
atcccggcgcgcgatgtcgtcgggagatggcgccgcctgggaagccgccgagagatatcagggaagatcgtctgatttc
tcctcggatgccacctcatctctcgagtttctccgcctgttactccctgccgaacctgatatttcccgttgtcgtaaagagatgtt
tttattttactttacaccgggtcctctctctctgccagcacagctcagtgttggctgtgtgctcgggctcctgccaccggcggcc
tcatcttcttcttcttcttctctcctgctctcgcttatcacttcttcattcattcttattccttttcatcatcaaactagcatttcttactttat
ttattttttcaattttcaattttcagataaaaccaaactacttgggttacagccgtcaaca

FIG. 17.

tcgactctagttttgaaatccaaaaaaaaaacaaagttcaataaaatgttacccaattgtgcgattttgctttaaaaatacggta
cccggtctcgatgcggcaattgtttggtaaatgtaaaagggtgtgcgcctttaaagagtactgtaatttcaatcttccgacactg
ctgaatttttattgactttttgttcattaatttatatatgatttattggtatgttaaaaaaacacccattttcaaatctattaaaattccac
aacaacaaaagttcgagattacagtacttttagaggcgcacatcctttttgggatactaaacaattgtcgcgtcgagaccag
gtaccatatttccaaaacacaatttcgcgtgtaaataaaaaatatcaacataataatttccatttttcgaaatttaaagttaatcact
ttttggtttagattatgatttcacacgtttttttccttctagttctctttttttgttatttgcctgaaaaatggtctgaaaacttaggcaat
cagcaatgtgtcacataatttctcccagagaaatcccttttcaacaaaatctcccggattgacctgtgtgctcgaccttgataaat
tggttggcagctctctggcttatcttttgagaggaaaaagatccaacaaattttatctccccttatcccttttctcttcatcactacc
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acttttcaaatcgaaataaaagagcatctgtcgctttttatcgatgtgcttctgtgagactaaagaactactcgttttcactcgttct
ctctctctcaactatcaaagttttgttgattgcgtgtgtcagcttccttctttttattatcatcttttcattggaggaaaaaaataacttc
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----ttccaatgaaaaaataaatacgtgcaattagttggtaatatgtgtacatgatgtaacttaaaacactacgttccat----

FIG. 17(CONTD 1).

atcacacgtcccccgcgccgagttttatagtttcattaataactttcggtttttgataatactaattgagttttattaattgtttccata
ttcatctagcactttgacctgtccttcttcgaattctcaaatatttgcactctgggtttaggtgtgaaaagaattgtcgtcattaagc
ggggcatccggggcaccgaaaaagccctccgattttaacgaatttgagataaagttggagagagagcccagtgtttgctt
gcccaagatatatatcttggatttatcaattactgtttgtcaacctgtcgccggcgcccccttttgctcttgctcccacgccccg
agattgaatttcaattttatttcgaagtaagtctcttgattgtttcgaaaatccgatgacagttttcattactttttgtctgttgattttg
tagggaaacattgaaattttctgatctttctttgatcttatgatttttcatttattccaattaaaaaaaattagcgcattcagaaccag
agtgaagcttgagatgttgtaggtttatcaaaagatcaaaatctcgaattccttcgaaatgtttttagttttcgacttccgtgtgatt
tctagcgatcctgacagagatcactgaattttaatgttatcgagattgttgtgtaggctccatctcctctctgaagcttctgattttg
ccgaaagtctagttacttgccgactgctgacactaggatatcccactaccgtacccattgttggatccgtactctgctgcgact
tcttctctgtttcacgtgaacctccgggatcgtcggtaagccccgcccgttatctgtgccaacttgtcttcgtgccctcgagcg
acgagctcattcaatcacgccacgacctccgtctggacagatgctctcattgtctctgcgtctccaagtattcgtcacactatct
catgcattctattcaaaacgcgagagaaagcgcgggaacgagagagagttcagacagatcgaacttgtttttatccccccc
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gcgcgagcatttccttctttgacttctctctttccgccaaaaagcctagcatttttattgataatttgattacacacactcagagttc
ttcgacatgataaagtgtttcattggcactcgccctaacagtacatgacaagggcggattattatcgatcgatattgaagacaa
actccaaatgtgtgctcattttggagccccgtgtggggcagctgctctcaatatattactagggagacgaggagggggacct
tatcgaacgtcgcatgagccattctttcttctttatgcactctcttcactctctcacacattaatcgattcatagactcccatattcct
tgatgaaggtgtgggtttttagctttttttcccgatttgtaaaaggaagaggctgacgatgttaggaaaaagagaacggagcc
gaaaaaacatccgtagtaagtcttccttttaagccgacacttttagacagcattcgccgctagttttgaagtttaaattttaaaaa
ataaaaattagtttcaatttttttaattactaaataggcaaaagtttttcaagaactctagaaaaactagcttaattcatgggtact
agaaaaattcttgttttaaattaatatttatcttaagatgtaattacgagaagctttttgaaaattctcaattaaaagaatttgccga
tttagaataaaagtcttcagaaatgagtaaaagctcaaattagaagtttgtttttaaaggaaaaacacgaaaaaagaacactat
ttatcttttcctccccgcgtaaaattagttgttgtgataatagtgatccgctgtctatttgcactcggctcttcacaccgtgcttcct
ctcacttgacccaacaggaaaaaaaaacatcacgtctgagacggtgaattgccttatcaagagcgtcgtctctttcacccagt
aacaaaaaaaatttggtttctttactttatatttatgtaggtcacaaaaaaaaagtgatgcagttttgtgggtcggttgtctccaca
ccacctccgcctccagcagcacacaatcatcttcgtgtgttctcgacgattccttgtatgccgcggtcgtgaatgcaccacatt
cgacgcgcaactacacaccacactcactttcggtggtattactacacgtcatcgttgttcgtagtctcccgctctttcgtcccca
ctcactcctcattattccccttggtgtattgatttttttaaatggtacaccactcctgacgtttctaccttcttgtttccgtccattta
gattttatctggaaatttttttaaaatttaggccagagagttctagttcttgttctaaaagtctaggtcagacatacattttctatttct
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cctcgcttgtttctcaaaatatgagatcaacggatttttttccttctcgattcaatttttttgctgcgctctgtctgccaaagtgtgtgtg
tccgagcaaaagatgagagaatttacaaacagaaatgaaaaaaagttggccaaataatgaagttttatccgagattgatggg
aaagatattaatgttctttacggtttggagggggagagagagatagatttttcgcatcaaactccgccttttacatgtcttttagaat
ctaaaatagattttttctcatcattttttaatagaaaatcgagaaattacagtaatttcgcaatttttcttgccaaaaatacacgaaattt

FIG. 17 (CONTD 2).

gtgggtctcgccacgatctcggtcttagtggttcatttggtttaaaagtttataaaatttcaaattctagtgtttaatttccgcataat
tggacctaaaatgggtttttgtcatcattttcaacaagaaatcgtgaaaatcctgttgtttcgcaatttttcttttcaaaaatacacga
aatatatggtaatttcccgaaatattgagggtctcgccacgatttcagtcacagtggccaggatttatcacgaaaaaagttcgc
ctagtctcacatttccggaaaaccgaatctaaattagtttttgtcatcattttgaacaaaaaatcgagacatccctatagtttcgc
aattttcgtcgcttttctctccaaaaatgacagtctagaattaaaattcgctggaactgggaccatgatatcttttctccccgttttt
cattttatttttattacactggattgactaaaggtcaccaccaccgccagtgtgtgccatatcacacacacacacacacacaat
gtcgagattttatgtgttatccctgcttgatttcgttccgttgtctctctctctattcatcttttgagccgagaagctccagagaat
ggagcacacaggatcccggcgcgcgatgtcgtcgggagatggcgccgcctgggaagccgccgagagatatcagggaa
gatcgtctgatttctcctcggatgccacctcatctctcgagtttctccgcctgttactccctgccgaacctgatatttcccgttgtc
gtaaagagatgtttttatttacttacaccgggtcctctctctctgccagcacagctcagtgttggctgtgtgctcgggctcctg
ccaccggcggcctcatcttcttcttcttcttctctcctgctctcgcttatcacttcttcattcattcttattcctttttcatcatcaaacta
gcatttcttactttatttatttttttcaattttcaattttcagataaaaccaaactacttgggttacagccgtcaacatggaggacgcg
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acgggtccggagggattgactccacagcaagttgaaacattgaggaacaaatatggagaaaatggttggtttttacatgga
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cgatcttctcgtcaagattctcctcctcgccgccatcatctcgtttgtgctcgcccttttcgaagagcacgaagatcagacaga
agcagtgacggcgttcgtcgaaccgttcgtcatccttctcattcttattgccaacgcgaccgtcggagtgtggcaggtagga
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gatagggaaaaagagtccctaaagaaaaaatagtgtaacgggcggtccggaagaaatgctctttgcgccgaaaagtttttg
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aaagatattgggtgatagaatagttgatggattgggctgcactatttgcctcaatttgccacaaatttccatctaatttgtcataat
tttccaggaacgaaatgctgaatcggccatcgaagcgctcaaggaatacgaaccagaaatggccaaggtcatccgatccg
gacaccacggaattcagatggttcgcgctaaggaactcgtgccaggagatc

FIG. 18.

atggaggacgcgcatgccaaagacgccaatgaggtgtgcaaattcttcggaacgggtccggagggattgactccacagc
aagttgaaacattgaggaacaaatatggagaaaatgaaatgcccgccgaagagggaaaatcactgtgggagctgattctc
gagcaattcgacgatcttctcgtcaagattctcctcctcgccgccatcatctcgtttgtgctcgcccttttcgaagagcacgaa
gatcagacagaagcagtgacggcgttcgtcgaaccgttcgtcatccttctcattcttattgccaacgcgaccgtcggagtgtg
gcaggaacgaaatgctgaatcggccatcgaagcgctcaaggaatacgaaccagaaatggccaaggtcatccgatccgg
acaccacggaattcagatggttcgcgctaaggaactcgtgccaggagatcttgtcgaagtttcagtcggagacaggatccc

FIG. 18 (CONT'D 1).

agccgatctccgtcttgtgaagatctactccaccaccatccgtatcgatcagtccatcctcaccggagaatctgtgtctgt atc
aagcacaccgactctgtgccagatccacgcgctgttaaccaggacaagaagaattgtctgttctcgggaaccaatgtcgca
tctggaaaggctcgtggaatcgtcttcggaaccggattgaccactgaaatcggaaagatccgtaccgaaatggctgagacc
gagaatgagaagacaccacttcaacagaagttggacgaattcggagagcaactttccaaggttatctctgttatttgcgttgct
gtttgggctatcaacattggacatttcaacgatccagctcacggtggatcatgggttaagggagcaatctactacttcaaaatc
gccgttgctcttgccgtcgctgctattccagaaggacttccagctgtcatcaccacgtgccttgccctcggaactcgccgtat
ggccaagaagaacgctattgtaagatcccttccatccgtcgaaactcttggatgcacatctgttatctgctctgacaagactg
gaactctcaccaccaaccagatgtctgtgtcaaagatgttcatcgctggacaagcttctggagacaacatcaacttcaccga
gttcgccatctccggatccacctacgagccagtcggaaaggtttccaccaatggacgtgaaatcaacccagctgctggaga
attcgaatcactcaccgagttggccatgatctgcgctatgtgcaatgattcatctgttgattacaatgagaccaagaagatcta
cgagaaagtcggagaagccactgaaactgctcttatcgttcttgctgagaagatgaatgttttcggaacctcgaaagccgga
ctttcaccaaaggagctcggaggagtttgcaaccgtgtcatccaacaaaaatggaagaaggagttcacactcgagttctcc
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FIG. 19.

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FIG. 20.

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FIG. 21.

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FIG. 22.

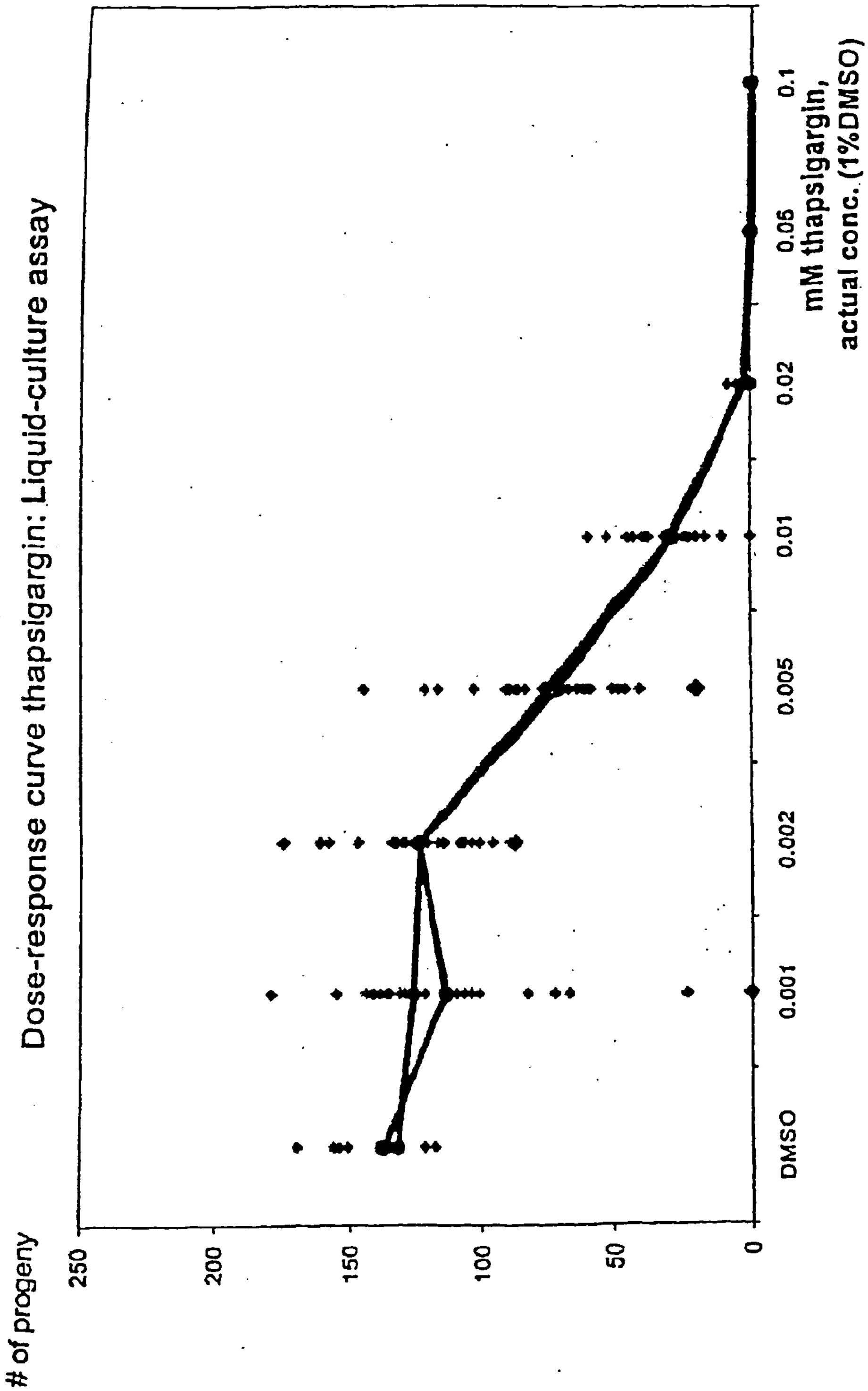
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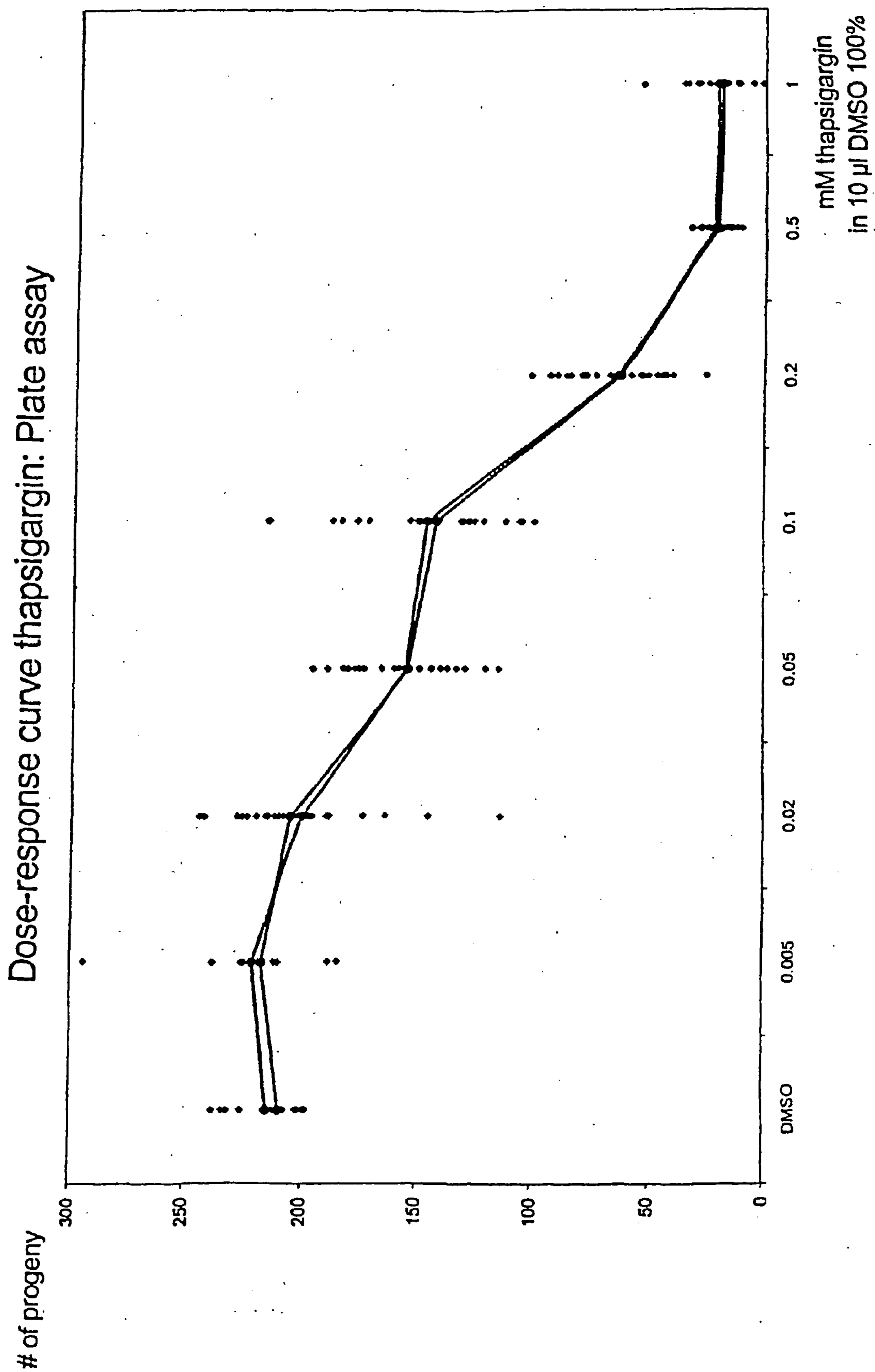
FIG. 23.



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<210> 16
<211> 3180
<212> DNA
<213> Caenorhabditis elegans

<400> 16
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cccgccgaag agggaaaatc actgtgggag ctgattctcg agcaattcga cgatcttctc 180

gtcaagattc tcctcctcgc cgccatcatc tcgtttgtgc tcgccctttt cgaagagcac 240

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atggttcgcg ctaaggaact cgtgccagga gatcttgtcg aagtttcagt cggagacaag 480

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<210> 17
<211> 837
<212> DNA
<213> Caenorhabditis elegans

<400> 17
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gaagagcact ttgcgcgcac acactgtact cattgttctg gataaaattc tctcgttgtt 420

tgccgtcgga tgtctgcctc tctgccattg agccggcttc ttcactatct ttagttaacc 480

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<210> 18
<211> 2396
<212> DNA
<213> Caenorhabditis elegans

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gcataatttg tcacgtgcca tagttttaca ttccactacg tcatagttct taaaatacta 180

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acaatcagtg ttttcaggat tatgtgatga actagatctt caagtttcgt tacatttcat 480

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<210> 19
<211> 45
<212> DNA
<213> Caenorhabditis elegans

<400> 19
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<210> 20
<211> 30
<212> DNA
<213> Artificial sequence

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<400> 20
cgatggatcc atggaagacg cctacgccag 30

<210> 21
<211> 29
<212> DNA
<213> Artificial sequence

<220>
<223> Arabidopsis SERCA reverse primer

<400> 21
cgatgggccc ctacttgtca cgccggtcc 29

<210> 22
<211> 33
<212> DNA
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<220>
<223> Heliothis SERCA forward primer

<400> 22
cgatggatcc atggaggacg ctcactcgaa atc 33

<210> 23
<211> 31
<212> DNA
<213> Artificial sequence

<220>
<223> Heliothis SERCA reverse primer

<400> 23

cgtagggccc ttacagcttc cacgtcggct g 31

<210> 24
<211> 23
<212> DNA
<213> Artificial sequence

<220>
<223> SERCA P2 primer

<400> 24
cgaagagcac gaagatcaga cag 23

<210> 25
<211> 19
<212> DNA
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<220>
<223> SERCA P8 primer

<400> 25
gagaggcggt tggtttggg 19

<210> 26
<211> 22
<212> DNA
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<220>
<223> SERCA P4 primer

<400> 26
ccgttcgtca tccttctcat tc 22

<210> 27
<211> 20
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<213> Artificial sequence

<220>
<223> SERCA P7 primer

<400> 27
cgacagatgg accgacgagc 20

<210> 28
<211> 32
<212> DNA
<213> Artificial sequence

<220>
<223> Degenerate primer ID1

<400> 28
acccctctga agaagaagct graygartty gg 32

<210> 29
<211> 23
<212> DNA
<213> Artificial sequence

<220>
<223> Degenerate primer ID2

<220>
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<223> "n" represents "g, a, t or c"

<400> 29
gccgtggccg ccathccnga rgg 23

<210> 30
<211> 27
<212> DNA
<213> Artificial sequence

<220>
<223> Degenerate primer ID3

<220>
<221> misc_feature
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<400> 30
caccgtgatc tgctccgaya aracngg 27

<210> 31
<211> 25
<212> DNA
<213> Artificial sequence

<220>
<223> Degenerate primer ID4

<220>
<221> misc_feature
<222> (17)..(17)
<223> "n" represents "g, a, t or c"

<400> 31
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<210> 32

<211> 30
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<213> Artificial sequence

<220>
<223> Degenerate primer ID5

<220>
<221> misc_feature
<222> (25)..(25)
<223> "n" represents "g, a, t or c"

<220>
<221> misc_feature
<222> (28)..(28)
<223> "n" represents "g, a, t or c"

<400> 32
ccggtacatg atctcctcca ayrtnggnga 30

<210> 33
<211> 25
<212> DNA
<213> Artificial sequence

<220>
<223> Degenerate primer ID6

<220>
<221> misc_feature
<222> (17)..(17)
<223> "n" represents "g, a, t or c"

<400> 33
tggtggtcag ggtgccngty ttrtc 25

<210> 34
<211> 24
<212> DNA
<213> Artificial sequence

<220>
<223> Degenerate primer ID7

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<223> "n" represents "g, a, t or c"

<220>
<221> misc_feature
<222> (22)..(22)
<223> "n" represents "g, a, t or c"

<400> 34
gttcacgccg tcgccngtca tngc 24

<210> 35
<211> 28
<212> DNA
<213> Artificial sequence

<220>
<223> Degenerate primer ID8

<400> 35
cctcgccgat gttggagswd atcatrta 28

<210> 36
<211> 28
<212> DNA
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<220>
<223> Degenerate primer ID9

<220>
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<210> 39
<211> 32
<212> DNA
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02391

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, PAJ, MEDLINE, SCISEARCH, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAHANEY JAMES ET AL: "Phospholamban reduces cardiac Ca-ATPase sensitivity to thapsigargin and cyclopiazonic acid." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 372, no. 2, 15 December 1999 (1999-12-15), pages 408-413, XP001055979 ISSN: 0003-9861	48-56, 59-62
Y	the whole document	1-62

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2002	20/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreno de Vega, C

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB 01/02391

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y,P	WAGGONER JASON R ET AL: "Fluorescence studies of the cardiac Ca-ATPase expressed in insect cells: Effect of phospholamban on Ca-ATPase conformational states." BIOPHYSICAL JOURNAL, vol. 80, no. 1 Part 2, January 2001 (2001-01), pages 432a-433a, XP001057572 45th Annual Meeting of the Biophysical Society;Boston, Massachusetts, USA; February 17-21, 2001 ISSN: 0006-3495 the whole document ---	1-62
Y	PERIZ, G. AND FORTINI, M.E.: "Ca2+-ATPase function is required for intracellular trafficking of the Notch receptor in Drosophila" EMBO, vol. 18, no. 21, 1999, pages 5983-5993, XP001061694 cited in the application the whole document ---	1-62
Y	WO 90 09096 A (CAMBRIDGE NEUROSCIENCE RESEARCH, INC) 23 August 1990 (1990-08-23) the whole document ---	1-62
Y	WO 00 34438 A (DEVGEN NV) 15 June 2000 (2000-06-15) claims 1-111 ---	1-62
X,P	GB 2 349 217 A (DEVGEN NV) 25 October 2000 (2000-10-25) the whole document -----	2-32, 34-46, 48-57, 59-62

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 62 relates to a compound defined by reference to its activity in a method of screening

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in the description at page 51.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 01/02391

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9009096 A	23-08-1990	AU 5106790 A	05-09-1990
		WO 9009096 A2	23-08-1990
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		GB 2359360 A ,B	22-08-2001
		GB 2359361 A ,B	22-08-2001
		WO 0063426 A2	26-10-2000
		WO 0063427 A2	26-10-2000